Medical Library JUL 3 1939

JOURNAL OF NEUROPHYSIOLOGY

J. NEUROPHYSIOL.

EDITORIAL BOARD

J. G. DUSSER de BARENNE

J. F. FULTON R. W. GERARD

ADVISORY BOARD

E. D. ADRIAN (Cambridge)
PERCIVAL BAILEY (Chicago)
PHILIP BARD (Baltimore)
G. H. BISHOP (St. Louis)
F. BREMER (Brussels)
DETLEV W. BRONK (Philadelphia)
E. VON BRÜCKE (Boston)
STANLEY COBB (Boston)
HALLOWELL DAVIS (Boston)
U. ERBECKE (Bonn)
J. C. ECCLES (Sydney)
JOSEPH ERLANGER (St. Louis)
WALLACE O. FENN (Rochester)
ALEXANDER FORBES (Boston)
H. S. GASSER (New York)
RAGNAR GRANIT (Helsingfors)
W. R. HESS (Zürich)
MARION HINES (Baltimore)
DAVENPORT HOOKER (Pittsburgh)
R. LORENTE DE NÓ (New York)
WILDER PENFIELD (Montreal)
H. PIÉRON (Paris)
S. W. RANSON (Chicago)
C. S. SHERRINGTON (Ipswich)

JULY 1939

VOL. II ISSUED BI-MONTHLY NO. 4

PUBLISHED BY CHARLES C THOMAS

220 EAST MONROE STREET, SPRINGFIELD, ILLINOIS, U.S.A.

JOURNAL OF NEUROPHYSIOLOGY

SCOPE: The aim of the *Journal of Neurophysiology* is to provide a channel for *prompt* publication of original contributions on the functions of the nervous system, peripheral and central. Materials submitted may include any phase of the subject amenable to experimental analysis; papers on pure morphology or neuropathology are not acceptable. Clinical, psychological and zoological studies will be considered only if primarily experimental in character.

MANUSCRIPTS: Manuscripts should be addressed to THE EDITORS, JOURNAL OF NEUROPHYSIOLOGY, 333 Cedar Street, New Haven, Connecticut, U.S.A. Papers should be concise and submitted in typewritten form, preferably in triple space, with tabular matter and passages for small print in double space and on separate sheets. All materials should be mailed flat. A brief summary should be included.

REFERENCES: Citations of literature, in alphabetical order and typed on a separate sheet, should include names and initial(s) of the author(s) with *full title* and full pagination of the book or paper. Citations of books and monographs should include also publisher, place and year. Names of journals should be abbreviated in accordance with the system used in *A world list of scientific periodicals published in the years 1900–1933* (Oxford University Press, 1934). For other details of form see the references in this number. References may be cited in the text by year or by elevated numerals.

A Style Book for the *Journal* will be supplied free of charge to contributors; additional copies may be purchased at 25 cents each.

COSTS CHARGEABLE TO AUTHORS—*Illustrations*: The allowance for free illustrations varies with the length of the paper and the character of the illustrative matter, but not more than four 3×3.5 inch half-tones (or their equivalent in area) will be allowed free to any contributor. When a paper has been accepted for publication, authors will be notified promptly of any charges for illustrations in excess of the free allowance. These will be charged to the author at a rate of approximately $5.00 for a 3×3.5 inch (7.6×8.9 cm.) half-tone and at a somewhat lower rate for zinc cuts. All illustrations, especially photographs, should be sharp and clear and submitted ready for reproduction, *i.e.*, with lettering, mounting and arrangements of figures completed.

Special typography. Tables, mathematical and chemical formulae and also text set up in small print (8 point) in excess of 10 per cent of composition costs are chargeable to the author.

Proof corrections. Corrections in galley proof will be allowed without charge up to 5 per cent of the original cost of composition of 10 point type. The cost of changes in page proof, if made by the author, will be borne by him. *Page proof* will be submitted to authors only when special questions arise. Manuscripts and figures will be returned after the editorial office has corrected page proof.

Reprints. Twenty-five reprints of each paper will be supplied without charge; larger numbers can be purchased at cost; delivery will be prompt. Reprints should be ordered on forms accompanying the galley proof and returned with it to the Editorial Office.

SUBSCRIPTIONS: The subscription rate for the volume of six bi-monthly issues is $6.00 in the United States, Canada and Latin America, and $6.50 in other countries. It is payable in advance to the publisher: CHARLES C THOMAS, 220 East Monroe Street, Springfield, Illinois, U.S.A.

Entered as second-class matter February 13, 1939, at the postoffice at Springfield, Illinois, and Menasha, Wisconsin under the Act of March 3, 1879

COPYRIGHT, 1939 BY CHARLES C THOMAS

CEREBRAL BLOOD FLOW DURING INDUCED EPILEPTIFORM SEIZURES IN ANIMALS AND MAN*

WILDER PENFIELD, KÁLMÁN VON SÁNTHA AND ANDRÉ CIPRIANI
Department of Neurology and Neurosurgery, McGill University and the Montreal Neurological Institute, Montreal

(Received for publication January 28, 1939)

THE MECHANISM of an epileptic seizure presents a complicated physiological problem that should be studied in the epileptic patient and supplemented by analysis of experimental seizures in animals. The modification by Gibbs[4] of the thermoelectric method of measuring blood flow has provided a technique of study of the cerebral circulation during seizures in animals which has been adapted with few changes to an analogous study of epileptics during craniotomy. Preparatory to our use of the method von Sántha and Cipriani[11] used it with certain minor modifications to analyze simple motor responses in animals. They found that increased function (non-convulsive) produced by cortical stimulation, was associated with temporary increase of local blood flow. Recently Gibbs[1] and Gibbs, Lennox and Gibbs[2] have used the technique to analyze blood flow in the parietal cortex of animals and the rate of flow through the jugular vein of man during epileptiform seizures. They found no evidence of decreased blood flow preceding an attack thus excluding a generalized cerebral ischemia at this time. They concluded also that during a seizure there was a greater total cerebral blood flow.

Approaching the problem from a different point of view and using different material our results nevertheless conform in a general way to theirs. We can also add further details in regard to delimitation of convulsive discharge and interpretation of the discharge mechanism.

EXPERIMENTAL STUDIES

In our experiments seizures were induced by electrical stimulation instead of by convulsant drugs. Thus we knew the focus of initiation of each convulsion and there was no question of the direct effect of a drug on the vascular system. A response was considered to be convulsive when it continued or spread after the cessation of cortical stimulation. The blood flow in different areas of the brain was measured with one or two of Gibbs' heated thermocouples with certain precautions to be mentioned below.

TECHNIQUE

Cats (35 in number) and monkeys (15 in number) were used, as a rule under Dial anesthesia although several of the monkeys were operated upon under local nupercaine

* Portion I is experimental and this work was carried out largely by two of us, Kálmán von Sántha and André Cipriani. Portion II contains an analogous study of epileptic seizures in man for which Wilder Penfield is chiefly responsible.

anesthesia. The dose of Dial given intraperitoneally was 0.4–0.5 cc. of a 10 per cent solution per kg. for cats, and 0.4 cc. for monkeys. In several cases the anesthesia was made lighter in order to increase the excitability of the cortex for electrical stimulation. This was done by the administration of intravenous metrazol (0.2–0.5 cc. of a 10 per cent solution). In most of the experiments a unilateral left craniotomy was performed, in the remainder the skull was opened bilaterally. The heated couple was inserted into the exposed cortex or in some deep structure of the brain. In the case of a deep structure its position was later verified by autopsy. In the early experiments the fixed temperature junction was placed in an indifferent part of the brain. Later on it was immersed in a thermos bottle filled with melting ice. The alterations in the temperature of the tip of the couple produced by changes in blood flow were recorded on a kymograph drum together with blood pressure and respiration.

Owing to the sensitivity of the recording device (0.0025°C. per mm. deflection) a series of experiments was conducted in order to account for and to eliminate artefact with the following results: When the heated couple was placed in grey matter 1 or 2 mm. below the brain surface it was necessary to shield the operative field from draughts. The shield used was partly made of glass so that the cortex could be observed, and a bipolar electrode was incorporated in the shield in such a manner that the cortex could be stimulated over its exposed surface without the removal of the shield. In these preliminary control experiments the stimulating current* heated the tissue around the electrode to an appreciable extent: thus stimulation close to the couple could simulate a decrease in blood flow. With this in view a minimum stimulating voltage was always used without stimulating too close to the couple. We further observed that the circulating blood was at a higher temperature than the superficial layers of the exposed cortex. Thus the heated couple when inserted superficially could indicate either an increased or decreased blood flow depending on whether it was at a higher or a lower temperature than the circulating blood. The proper temperature for the tip of the thermocouple should be checked in each case by the preliminary use of adrenalin and histamine intravenously; the former could always be relied upon to increase the cerebral circulation and the latter to decrease it under Dial anesthesia.

Results

Experiments type 1 (*Monkeys*). The thermocouple was placed within the grey matter of the middle third of the precentral gyrus corresponding to the inferior part of the hand area. When contralateral leg movements were produced by stimulation of the leg area the galvanometer showed no change in blood flow. When the cortex just above the sulcus precentralis inferior was stimulated, eliciting hand and arm movements, a definite increase in circulation was recorded. A more marked increase in circulation resulted from stimulation of the cortex lying above the sulcus precentralis superior when there was a 35 second after-discharge involving the contralateral hand, arm and trunk. It should be pointed out that the three stimulation points mentioned above were practically equidistant from the thermocouple. Thus the phenomenon cannot be attributed to proximity of the stimulating electrode.

Experiments type 2 (*Monkeys*). A bilateral craniotomy was performed. The couple was placed in the left motor cortex. An increase in blood flow was recorded when unilateral right-sided convulsions resulted from stimulation of the left motor or premotor cortex (IL in Fig. 1). On the other hand there was no significant change when a seizure was produced on the left by right motor and premotor stimulation, but the blood flow record alterations were simply parallel to those of the systemic blood pressure (CL Fig. 1).

On increasing the intensity of the stimulus, or on raising the excitability of the cortex with metrazol generalized convulsions followed unilateral cortical stimulation (Fig. 1), in which case a blood flow increase was recorded in the left motor cortex irrespective of the side from which stimulation had precipitated the fit (Fig. 2). There was no difference in the magnitude of the circulatory change but there was a delay of a few seconds in the change resulting from right-sided stimulation. The results were the same whether the fit had been produced by stimulation of the motor, premotor or postcentral cortex.

Experiments type 3. The thermocouple was placed in the premotor cortex, the postcentral cortex and outside of the sensorimotor cortex. Generalized convulsions were pro-

* The stimulating current was from a thyratron, "a universal precision stimulator" described by Schmitt and Schmitt (*Science*, 1932, *76:* 328).

duced. In monkeys the premotor and postcentral cortex showed circulatory changes similar to those found in the precentral cortex, with no delay on ipsilateral stimulation. The area rostral to the premotor cortex, *i.e.*, areas 8, 9c and 9d, showed smaller changes with a definite delay. This difference was even more marked in area 10a. The orbital cortex revealed no definite increase in blood flow. No circulatory change was recorded in area 7 of cats. In area 7 of monkeys (gyrus supramarginalis) there was increased circulation when a generalized fit was produced by stimulation of the ipsilateral postcentral gyrus. Only a small change occurred when a similar fit was produced from the contralateral side.

We must conclude that the change in the supramarginal gyrus resulting from ipsilateral stimulation resulted from some intracortical connection and was not related to the

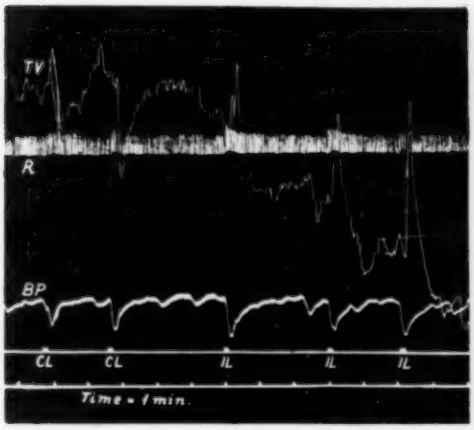


FIG. 1. (Expt. 1590.) Changes in blood flow of the left motor cortex (monkey) associated with unilateral seizures produced by stimulation of contralateral (CL) and ipsilateral (IL) precentral gyrus. TV = temperature variations of couple, a fall in the curve indicating decreased flow and a rise the reverse. BP = systemic blood pressure taken from femoral artery. R = respiration.

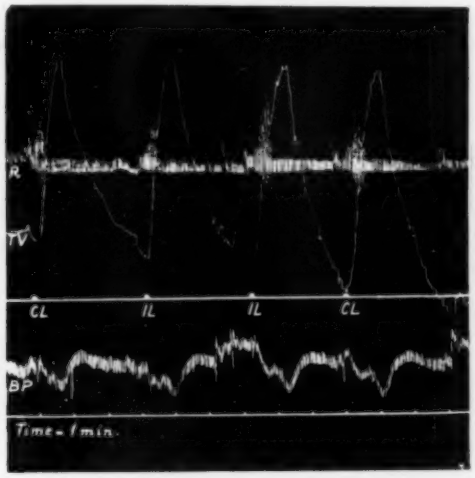


FIG. 2. (Expt. 1590.) Blood flow changes in the left motor cortex (monkey) after contralateral (CL) and ipsilateral (IL) stimulation of the frontal cortex lying just anterior to the precentral gyrus, resulting each time in a generalized convulsion. These results were obtained after the animal was sensitized with metrazol. Sensitivity of blood flow recorder one-third of that in Fig. 1. TV = temperature variations of couple resulting from blood flow change; rise of curve indicates increased blood flow. BP = blood pressure taken from the femoral artery. R = respiration.

seizure. In a few cases the effect of stimulation of areas lying outside the sensorimotor field on the circulation of the motor cortex was studied. No circulatory change was observed in the motor cortex when areas 10a, 9a, 5 and 7 were stimulated.

Experiments type 4. The thermocouple was placed in some of the subcortical ganglia, tha caudate nucleus and the thalamus of cats, the thalamus, putamen and pallidum of monkeys. During generalized convulsions these subcortical centers showed a marked increase in circulation, greater even than that observed in the cortex. In cats following contralateral stimulation, which produced a unilateral motor response, there was no circulatory change in the caudate and thalamus. A similar ipsilateral stimulation produced a marked increase in circulation. In one monkey we were able to conduct such an experiment in the pallidum with similar results.

When there was a generalized convulsion the change in blood flow in the above ganglia was the same whether the left or right motor cortex initiated the seizure. We also observed

and have described elsewhere[11] that only certain parts of the thalamus showed a circulatory change in response to motor stimulation on the ipsilateral side. In the pulvinar and nucleus lateralis posterior no significant change could be observed.

Experiments type 5 (Monkeys). In a few cases we were able to record blood flow in monkeys during spontaneous fits. The animals were given metrazol intravenously which was followed by a severe convulsion. After this generalized convulsions could be produced by weak electrical stimulation. These electrical fits lasted from a half to one minute. Subsequently the animals continued to have seizures at about 5 minute intervals without stimulation. We recorded changes of blood flow in the motor cortex, the putamen and the medial nucleus of the thalamus. There were no pre-convulsion phenomena and the blood flow record differed in no way from that elicited by stimulation of the motor cortex. The subcortical ganglia again showed a greater reaction than the cortex.

In interpreting the records obtained in the brain we have paid special attention to the nature of the tissue surrounding the thermocouple. If the couple is entirely surrounded by white matter the changes are small and sluggish and tend to be influenced by the systemic blood pressure in a passive manner. In the subcortical centers the proportion of grey to white matter varies. In the cortex itself a thermocouple too deeply placed may be partially embedded in the underlying white matter, resulting in an apparently reduced reaction.

Discussion of experimental evidence

The alteration in blood flow measured by the thermo-electric method during convulsive seizures depends on the function of the surrounding tissue. Some areas of grey matter seem to play little or no rôle during a seizure, even a so-called generalized seizure. The circulation change depends further upon the structure of tissue and the capillary bed which surround the couple. According to Craigie[5], Cobb and Talbott[6] and Lindgren[7] the vascular supply of the grey and the white matter is altogether different. The grey matter shows considerable inequality in supply but the most poorly vascularized grey matter contains 50 per cent more capillaries than the best vascularized white matter. In general the sensory and intercalary centers are better vascularized than the motor centers. The cortex, particularly its fourth layer, is well vascularized. According to Spatz[8] the blood supply of the striatum is probably still more abundant. Dunning and Wolff[9] believe that the blood supply of a given center is directly proportional to the number of synapses. In the cerebral cortex the thermocouple is placed in a grey layer that is thin and superficial. In the thalamus the couple is deep and more completely surrounded. That these factors are relatively unimportant however, is shown by the injection of intravenous adrenalin which induces a similar increase of flow both in the cortical and subcortical centers. This is shown by the simultaneous tracings in Fig. 3.

Generalized electrical seizures and certain spontaneous seizures in animals are accompanied by increased circulation in certain parts of the brain. Reference to type 3 experiments above shows that outside of the sensorimotor cortex other areas of cortex may show little or no circulatory change when a fit is produced by stimulation in the sensorimotor area, and conversely stimulation in these outside areas fails to produce a seizure. Gibbs, Lennox and Gibbs[2] suggested that this blood flow change might be passive, due either to increased blood pressure, or to general increase of CO_2. According to our observations neither of these explanations would seem ade-

quate since we are obviously dealing with localized circulatory changes due to some focal cause. The only plausible explanation of this increased circulation, which begins from about 4–10 sec. after the first convulsive movement, and continues after the attack has ceased, seems to be the increased neuronal activity of the region in question. This augmented function must be associated with increased metabolism which in turn produces the chemical stimulus for the vasodilatation. The circulatory increase produced by a seizure is greater in the involved subcortical centers than in the involved cortex. The sluggish and small responses of the white matter are to be explained by poor vascularity and by low rate of metabolism.

Observations on Human Beings

A study of circulation during fits in man has been carried out over a period of two and one-half years whenever a suitable case presented the opportunity. The tiny thermocouple was embedded within the brain substance at operation. But inasmuch as the observations were always secondary to more urgent clinical problems only a few of the records are above criticism and therefore suited to the present study. At the beginning we were assisted by Dr. Norcross whose experimental work on blood flow has already been published.[3]

The operative procedure employed for cortical exploration of selected cases of focal epilepsy and the therapeutic results have been outlined elsewhere by Penfield.[10] A large area of one hemisphere was exposed under nupercaine analgesia. Electrical exploration was then carried out with a bipolar or unipolar electrode using the thyratron stimulator employed in the experimental study described above. The kymograph drum galvanometer and recording apparatus were set up in an adjoining room and the time of stimulation, of onset of seizure, etc. were signalled directly to the drum by an observer in the operating theater.

Fig. 3. Blood flow increase in the putamen and cortex (monkey) after intravenous adrenalin (0.05 mgm). P = blood flow change in the putamen. C = blood flow change in the cortex. R = respiration. BP = blood pressure taken from the femoral artery.

Case 1. F.H. A young man of 25 years received a head injury 2 years before operation. Focal seizures appeared 6 months later. A large right osteoplastic craniotomy was carried out and a meningocerebral cicatrix was exposed involving the lower one-third of the Rolandic cortex. The thermocouple was inserted into the grey matter at point 1 Fig. 4. At E stimulation produced trembling in large finger and thumb of the contralateral hand;

at G there was "electrical" feeling in hand and wrist. Stimulation at O caused the patient to say suddenly "I got the feeling I get in my attacks, a twisting round feeling of the eyes." The one eye which could be seen by the observer closed, squinted and then looked upward.

Attack I. Stimulation repeated at O (Fig. 4) produced a slight attack. The patient cried "Oh" and for 45 sec. there was a good deal of emotion and he could not speak clearly. At 15 sec. he whispered "It felt like an attack. It felt as though the head were turning of its own accord."

Attack II. Stimulation at X continuing 3 sec. produced similar attack but a little

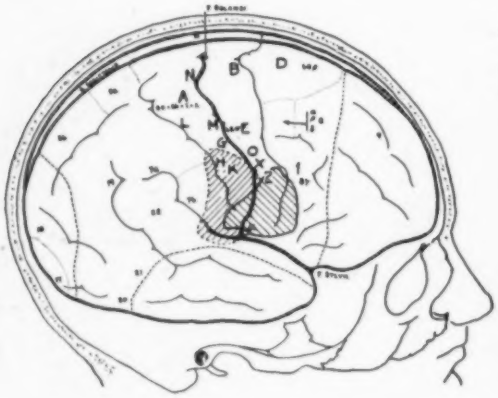


FIG. 4. (Case 1.) Thermocouple positions are represented by points 1 and 2. Letters refer to stimulation points. The shaded area is the approximate location of the epileptogenic lesion.

more severe. The thermocouple was now removed from point 1 and inserted into the cortex at a point 3 mm. below X, that is at point 2. The wire carrying the thermocouple was passed through the pia and obliquely inward 1.25 mm. so that the couple remained superficial. The act of inserting the couple which was now quite near the scar was sufficient to produce a moderately severe focal attack of 17 sec. duration similar to the others. No blood flow record was made of this.

Attack III. Stimulation at X produced a more severe attack but focal like the others. The patient said at the close "Same kind of attack," but his head and eye were turned forcibly to the left side and there were clonic movements of the left arm. Just before stimulation visible pulsation in the superficial arteries of the brain was quite active. All visible pulsation disappeared with the onset of the seizure and returned 11 sec. later. Pulsation on its return was violent as is usually the case.

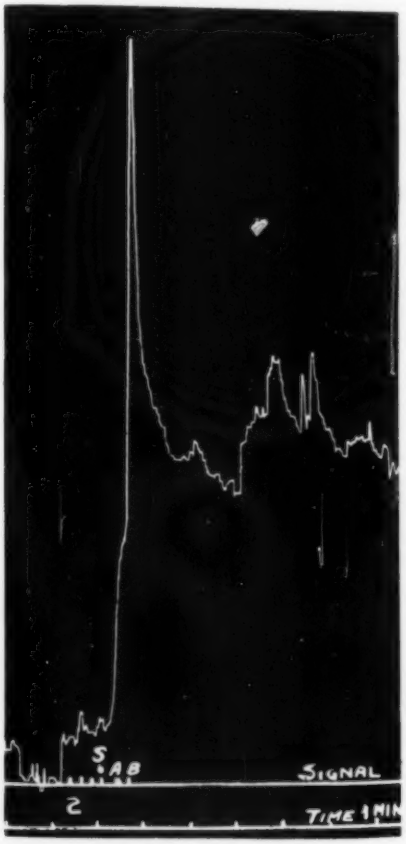


FIG. 5. (Case 1.) Attack III. Blood flow record with the thermocouple in position 2. Stimulation was at point X (Fig. 4) indicated by S on the signal line. The attack was recognized by the operator at A on signal line and was over at B.

The blood flow as measured at point 1 showed a small increase coincidental with Attack I. The increased flow was a little greater with Attack II. When the thermocouple was reinserted at point 2 the sensitivity of the flow record was purposely decreased but Attack III was associated with a marked increase in blood flow (Fig. 5) which reached its peak at 18 sec., during the time when visible arterial pulsation had disappeared. These were focal seizures. The warmed thermocouple was in the discharging area of cortex and it indicated more rapid cooling which is taken to mean greater flow of blood through the tissue during the seizure.

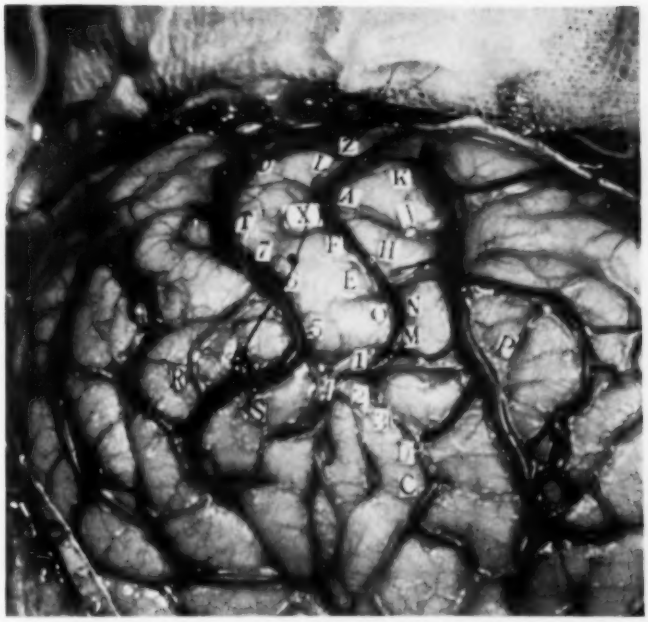


FIG. 6. (Case 2.) Photograph of the field at operation. The thermocouple with attached black wires can be seen inserted just above S and passing under ticket (X). The tickets were laid on the cortex to mark the sites from which electrical stimulation produced sensory or motor response.

CASE 2. M.M. A young man suffering from habitual epileptic seizures had a small traumatic lesion in the supramarginal gyrus. After right osteoplastic craniotomy the thermocouple was inserted to a depth of 1 mm. at the site of superficial injury (Fig. 6). Stimulation at X in the postcentral gyrus produced a focal attack characterized by loss of consciousness, turning of eyes to left and a little pulling of the mouth to the left. This lasted 7 sec. when he spoke again but it was followed almost at once by two repetitions of the attack each with conjugate deviation of the eyes. There was an associated increase of blood flow which was of somewhat longer duration than in the previous case. No change in the pulsation of the superficial arteries was observed.

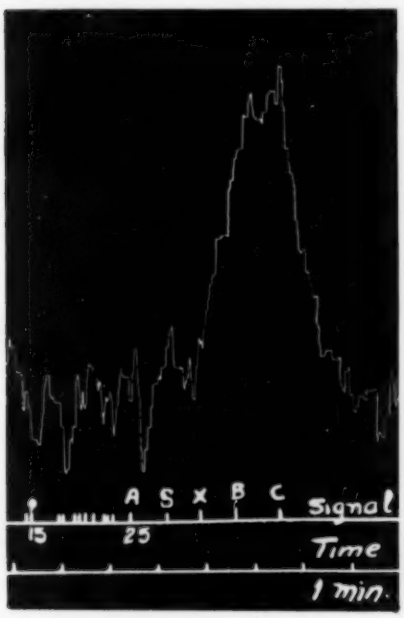


Figure 7 shows the blood flow record. At A on the signal line the cortex was stimulated at point A as shown by the ticket on the brain in Fig. 6. The result was sudden marked closure of the hand and flexion of the elbow. Stimulation was next carried out at X on the brain which corresponds with S on the signal line. This produced the seizure but the operator was only certain that it was a seizure about 40 sec. after stimulation when he signalled to the drum at point X on the signal line. At B and again at C the operator recognized that a second and a third small spontaneous fit were occurring and it is seen that there was a further increase of blood flow corresponding with each recurrence.

CASE 3. M.O. An example of blood flow record taken outside of the discharging area may be given. Here the thermocouple was placed in area 19 of the

FIG. 7. (Case 2.) Blood flow record during an attack resulting from stimulation at point (X) in Fig. 6. On the signal line the instant of stimulation is indicated by S, the time of recognition of fit at X.

parietal lobe 10 cm. from the stimulation point which was in area 6aβ in the frontal lobe. The attack was focal in nature consisting in contralateral movements of arm and face. There was no evidence of alteration in blood flow in the tissue about the thermocouple although the apparatus was recording satisfactorily as shown by the cooling effect each time the cortex was sprayed to keep it moist. This would suggest that the blood flow alteration is focal in a focal discharge.

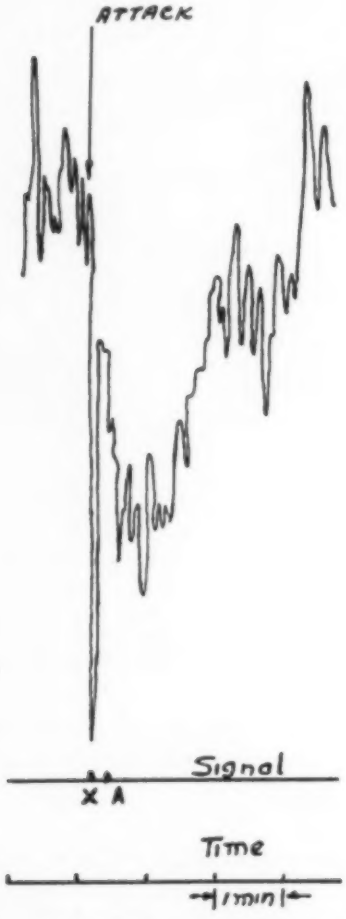


FIG. 8. (Case 4.) Blood flow record during an attack. X denotes instant of stimulation and A the end of the attack. For explanation of decrease in blood flow see text.

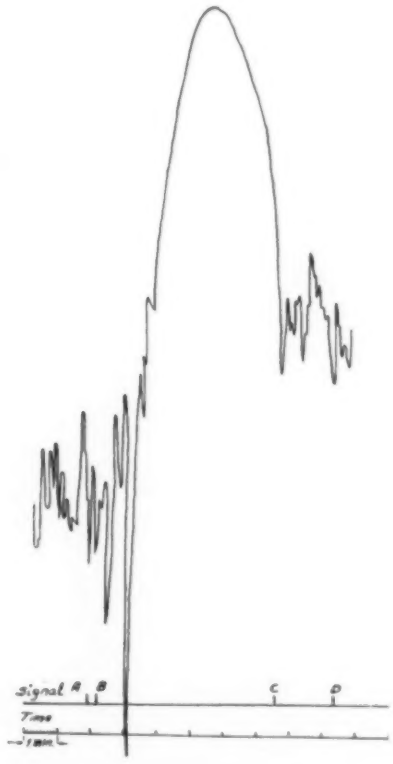


FIG. 9. (Case 5.) Blood flow record during an attack. Stimulation took place at A on the signal line. At B the attack was first recognized by the operator.

CASE 4. L.B. A young woman was found to have a deeply situated infiltrating tumor beneath the left postcentral gyrus. Stimulation of this gyrus however gave sensory responses with a lower threshold than the precentral. The thermocouple was placed in the frontal lobe 6 cm. anterior to the central fissure. A small focal attack produced by stimulation in the postcentral gyrus at a distance of 6 cm. was associated with no alteration in blood flow about the couple. A second attack however was produced by stimulation at a point 2 cm. posterior to the couple, the stimulation being continued for 7 sec. The attack lasted 8 sec. after its recognition which followed withdrawal of the stimulator and con-

sisted in clonic movements of the right upper extremity which the patient said resembled her habitual attacks.

The blood flow about the thermocouple showed a decrease (Fig. 8) rather than an increase. It may well be that the discharging state of the cortex which took origin at the point of stimulation spread only backward toward the central fissure and so never involved the tissue surrounding the thermocouple. If that surmise is correct then the temporary decrease in blood flow might indicate a contrary alteration of blood flow peripheral to the discharging area.

CASE 5. J.R. A young boy of 12 was subject to epileptic seizures beginning in the right hemisphere. The focus proved to be an area of circumscribed softening situated low down at the junction of the right temporal and occipital lobes. The thermocouple was placed in the lower postcentral convolution at a distance of about 12 cm. Only one attack was produced and that followed stimulation in the softened area mentioned above. The onset of the attack resembled that of his habitual major seizures. He swallowed, said he felt nauseated, vomited and his pupils were noted to be dilated. The pupils then contracted suddenly to a very small size, the eyes deviated slowly to the left, the face pulled to that side and he was apparently unconscious.

The thermocouple lying in the Rolandic cortex, which corresponds roughly with face representation, was a considerable distance from the stimulated focus. Convulsive movement of the face to the opposite side was the final phenomenon of the fit. The blood flow showed little alteration for almost a minute, then there was a sharp drop followed by a long continued increase of flow lasting over 4 min. (Fig. 9). The discharging state probably moved across the cortex toward the Rolandic region, as it usually does, so that the thermocouple was first on the outskirts and later within the area of epileptic discharge as the disturbance travelled forward. Here again there seems to have been slowing of circulation at the periphery.

GENERAL DISCUSSION

In chronic epileptics focal fits may be induced by electrical stimulation of the cortex which are outwardly identical with the habitual fits of the patient in question. During the seizure there is an increase in circulation within the circumscribed area of cortex which is involved in the "discharge" that produces the fit. This increase begins within the first minute after the precipitating stimulus with no preliminary decrease in flow and it outlasts the clinical evidence of the seizure. More distant areas of cortex may show no alteration in blood flow as in Case 3 above, or there may be a decrease in circulation of short duration at the periphery of the involved area of cortex as in Cases 4 and 5. Whether this peripheral decrease is an invariable phenomenon it is impossible to say from our limited observations. No initial decrease occurs at the focus where the attack begins.

In animals epileptiform seizures were accompanied by a constant circulatory increase in the motor cortex (using the term motor broadly). A similar but more marked increase has been observed in the caudatum, putamen, pallidum and thalamus. This blood flow increase appeared to be limited to the contralateral hemisphere in cases of unilateral convulsion. In generalized convulsion the change was equally present in both hemispheres. This increase in circulation started a few seconds after the first muscular movements and stopped soon after the attack was over. No significant circulatory change could be found in the white matter. The similarity in reaction between the unanesthetized human cortex and that of animals under Dial indicates that the Dial did not essentially alter the reactions in the

animal experiments and it further suggests that conclusions drawn from the experimental evidence may be applied to clinical epileptic seizures.

In the case of the experimental seizures we have concluded above that the change in circulation is secondary to the sudden increase in neuronal discharge taking place during the convulsion, and that this increase of neuronal activity was even greater in subcortical centers than it was in the cortex. This is in conformity with the findings of von Sántha and Cipriani[11] who showed that cortical stimulation which produces a simple motor response, without convulsive after-discharge, also produces a demonstrable increase in blood flow both in the cortex and in the related subcortical centers. The evidence of increased function both in the cortex and in the subcortical centers is contrary to the theory that would explain an epileptic convulsion as a release of subcortical centers from cortical control.

That there may occur in both the cerebrum and cerebellum of epileptic patients at some time vascular spasms is suggested by the well-known work of Spielmeyer and his pupils. Also it was pointed out by Penfield[14] that arterial constrictions are sometimes seen in the exposed epileptic cortex but that they appear after a convulsion and not during it. During an epileptic seizure in man the most frequently observed objective change in the brain is cessation of visible pulsation of pial arteries.[15] Whatever the explanation of this phenomenon may be, it is not due to decreased blood flow as shown in Attack III of Case 1 above. The evidence of our present communication indicates that vasospasm plays no rôle during a seizure nor is there evidence of widespread anemia following it. Vascular spasms and anemias may be concerned in the pathological background of epilepsy but at all events they play no rôle in the actual mechanism during a seizure.

Even though increased circulation does occur there is no reason to conclude that the enormously increased need for oxygen on the part of the neurones is completely satisfied (Penfield[15]). The tissues may still be in a state of severe anoxaemia. For example, a muscle suddenly called into use may double its circulation but if the muscle needs three times its resting circulation the muscle tissue will be in a state of functional anoxaemia.

Summary

Increased blood flow of the area of brain involved seems to be the invariable accompaniment of experimental convulsions in animals and of epileptic seizures in man. This change in blood flow does not apply to the whole brain and is therefore not a phenomenon secondary to changes in general circulation or respiration. The circulatory increase begins a little time after the onset of local neuronal discharge and may be interpreted as the direct result of increased ganglionic activity.

REFERENCES

1. Gibbs, F. A. Cerebral blood flow preceding and accompanying experimental convulsions. *Arch. Neurol. Psychiat., Chicago,* 1933, *30:* 1003–1010.
2. Gibbs, F. A., Lennox, W. G., and Gibbs, E. L. Cerebral blood flow preceding and

accompanying epileptic seizures in man. *Arch. Neurol. Psychiat., Chicago*, 1934, *32:* 257–272.

3. Norcross, N. Intracerebral blood flow: Experimental study. *Arch. Neurol. Psychiat., Chicago*, 1938, *40:* 291–299.
4. Gibbs, F. A. A thermoelectric blood flow recorder in the form of a needle. *Proc. Soc. exp. Biol., N.Y.*, 1933, *31:* 141–146.
5. Craigie, E. H. On the relative vascularity of various parts of the central nervous system of the albino rat. *J. comp. Neurol.*, 1920, *31:* 429–464.
6. Cobb, S., and Talbott, J. H. Studies in cerebral circulation; quantitative study of cerebral capillaries. *Trans. Ass. Amer. Phys.*, 1927, *42:* 255–262.
7. Lindgren, A. G. H. Quantitative Untersuchungen über den Kapillarengehalt der grauen Substanz des Gehirns bei jungen und alten Menschen. *J. Psychol. Neurol., Lpz.*, 1937, *47:* 492–509.
8. Spatz, H: cited by Jakob, A. *Die extrapyramidalen Erkrankungen*, Berlin, J. Springer, 1923.
9. Dunning, H. S., and Wolff, H. G. The relation between function and vascularity in the nervous system. *Trans. Amer. neurol. Ass.*, 1936, *62:* 150–154.
10. Penfield, W. Epilepsy and surgical therapy. *Arch. Neurol. Psychiat., Chicago*, 1936, *36:* 449–484.
11. Sántha, K. von and Cipriani, A. Focal alterations in subcortical circulation resulting from stimulation of the cerebral cortex. *Res. Publ. Ass. nerv. ment. Dis.*, 1937, *18:* 346–362.
12. Pike, F. H., Elsberg, C. A., McCulloch, W. S., and Chappell, M. N. The problem of localization in experimentally induced convulsions. *Arch. Neurol. Psychiat., Chicago*, 1930, *23:* 847–868.
13. Rovighi and Santini, Ziehen and Rothmann, cited by Graham Brown. *Handb. norm. path. Physiol.*, 1927, *10:* 418–524.
14. Penfield, W. The evidence for a cerebral vascular mechanism in epilepsy. *Ann. intern. Med.*, 1933, *7:* 303–310.
15. Penfield, W. The circulation of the epileptic brain. *Res. Publ. Ass. nerv. ment. Dis.*, 1937, *18:* 605–637.

ROLE OF THE SYMPATHETIC SYSTEM IN REFLEX DILATATION OF PUPIL*

BORIS URY AND ERNST GELLHORN
Departments of Physiology and Psychiatry, College of Medicine, University of Illinois, Chicago

(Received for publication February 20, 1939)

IN A preceding paper (Ury and Gellhorn) it was shown, in the rabbit, that the reflex pupillary dilatation produced by weak stimuli was solely due to an inhibition of the parasympathetic tone and not to an excitation of the sympathetic. The problem presented itself how far these results are applicable to other species under various conditions. The vast literature on this subject contains a wide disagreement concerning the rôle of the sympathetic and parasympathetic mechanisms in the pupillary dilatation in man and animals when pain stimuli are applied. Bechterew (1883), Braunstein (1894) and more recently Bain, Irving and McSwiney (1935) emphasize the importance of the inhibition of the parasympathetic, whereas Anderson (1904), Luchsinger (1880) and Dechaume (1937) claim that the sympathetic is responsible for the pupillary reaction since it is absent after the cervical sympathetic has been cut. Gellhorn and Darrow (1939) observed in cats that faradic stimuli applied to afferent nerves cause a dilatation of the normal and of the sympathectomized pupil, the former dilating somewhat more than the latter. Therefore, in addition to the inhibition of the parasympathetic which is fully established, the intact sympathetic either maintains a tonic innervation or is reflexly excited. The experiments reported here attempt to decide this question.

METHODS

The experiments were carried out on 9 cats placed in wooden boxes of special construction to allow a rigid fixation of the head. Faradic stimuli (Harvard inductorium with 3 v. in the primary circuit) were applied either with a different electrode on the paw and an indifferent one on a shaved area of the back, or with both on the exposed sciatic nerve. The lids were held wide open by a retractor and the pupils photographed with a 35 mm. movie camera. Two signal magnets recorded respectively the period of stimulation and the time when the individual pictures of the eyes were taken. The eyes were magnified 2.3 times but graphs in this paper are reduced to natural size.

The left third nerve was cut intracranially under nembutal narcosis. One week to two months later the animals were tested with a series of stimuli. Most cats were used repeatedly. In one the right cervical sympathetic was cut in addition to the left third nerve.

Since the pupil, after division of the third nerve, is wide if not maximally dilated, it is unsuited for the study of sympathetic action, but 1 to 2 drops of a 1 per cent eserine solution applied locally cause a constriction of the iris and permit the study of reflex dilatation. The threshold of pupillo-dilator fibers in the cephalad end of the divided cervical sympathetic is extremely low (secondary coil at 13 cm. and tilted to an angle of 80°) and is not altered by eserine, proving that this drug acts exclusively on the iris parasympathetic endings. A dilatation of the eserinized and parasympathectomized eye following a peripheral stimulus indicates sympathetic excitation; absence of such dilatation, when the normal eye

* Aided by a grant from The John and Mary R. Markle Foundation.

dilates, indicates that the action is exclusively through inhibition of the tonus of the third nerve. Further experiments were carried out on these cats after metrazol had been given in subconvulsive or convulsive doses, since this drug greatly increases the excitability of the sympathetic centers (Gellhorn and Darrow, 1939).

Results

The cat fastened in the wooden box frequently struggled and such movement was regularly accompanied by a dilatation of the normal or the

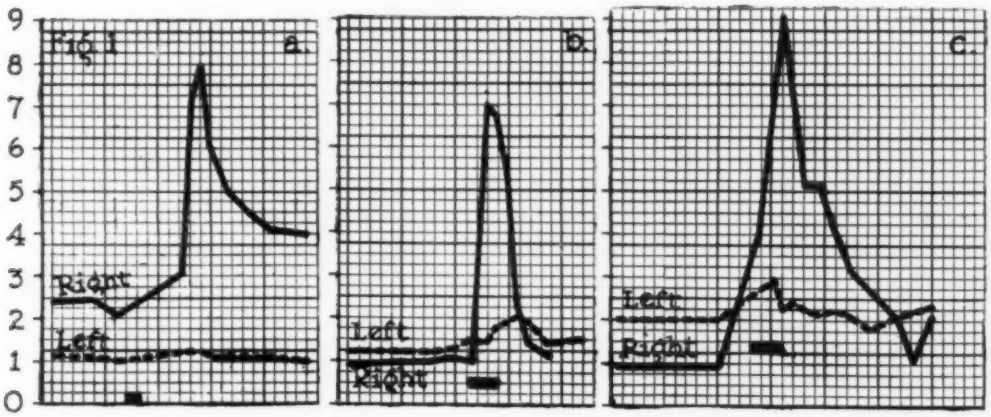


Fig. 1–5. ——— right normal eye; - - - - - left eye, the third nerve of which was cut; loca application of 1 per cent eserine.

Fig. 1. Cat, no narcosis. Stimulation of the paw of the left foot with faradic current. Harvard inductorium. 3 volts in the primary circuit. (a) Distance between primary and secondary coil, 6.0 cm.; 5 sec. (b) 5.0 cm.; 10 sec. (c) 3.0 cm.; 20 sec. In all these experiments struggling and vocalization.

sympathectomized pupil, but the parasympathectomized eserinized pupil never changed its size. Stimuli applied to non-narcotized and to etherized cats elicited, not only the pupillary changes to be described, but also general movements and vocalization. The parasympathectomized and eserinized pupil failed to dilate, however, except for a few slight responses (Fig. 1–3). Figure 1a shows the left parasympathectomized pupil to remain unchanged while the normal pupil dilates from 2 to 8 mm., on application of the faradic stimulus (5 sec. coil distance 6 cm.). Increase in intensity and duration of the stimulus (10 sec., 5 cm.) leads to less than 1 mm. dilatation on the left side, whereas the normal eye dilates from 1 to 7 mm. (Fig. 1b). Very powerful stimulation (20 sec., 3 cm.) leads to marked struggle and vocalization

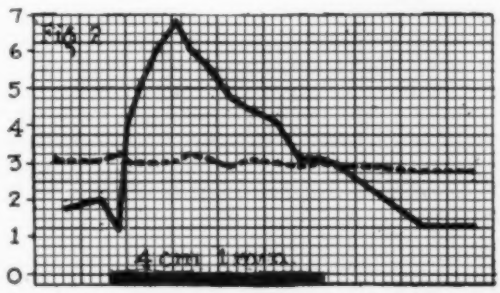


Fig. 2. Cat; deep ether narcosis, no movements, no vocalization. Stimulation of the paw 4 cm. for 60 sec.

and calls forth a large dilatation of the normal pupil but only a feeble one of the parasympathectomized pupil (Fig. 1c). Figure 2 shows complete absence of a sympathetic response to a stimulus which lasted 60 sec. and provoked a marked and prolonged dilatation in the normal eye. Figure 3 shows a maximal dilatation in the normal eye, from 2 to 13 mm., while the parasympathectomized pupil enlarged from 3 to 4 mm. Even the strongest stimuli produced no dilatation in the parasympathectomized eye in most experiments, and never one greater than 1 mm. (Fig. 1b, 1c, 3). Narcosis did not influence these results.

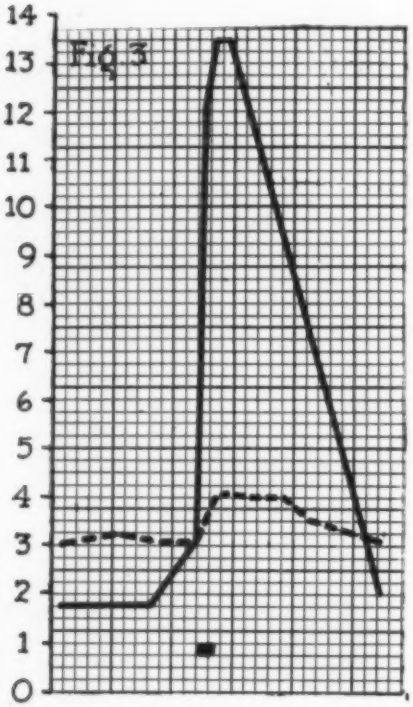


FIG. 3. Cat. Ether narcosis. Sciatic stimulated. 11 cm.; 5 sec.

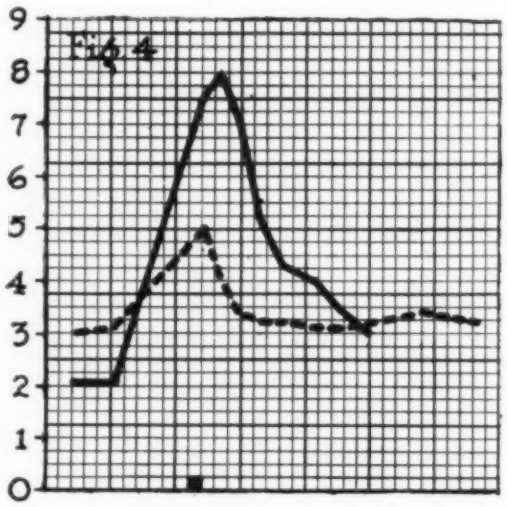


FIG. 4. Stimulation of the sciatic at 4 cm. distance for 3 sec. in light ether narcosis. Some movements and vocalization. The animal was injected with 65 mg. metrazol intraperitoneally prior to the stimulation. No convulsions.

Similar experiments after metrazol administration are illustrated in Fig. 4. In the presence of this drug the parasympathectomized eye responds to sciatic stimulation to a greater extent than in its absence, but the dilatation is still but a small fraction of that shown by the normal eye. When strong sympathetic impulses are present they will cause a dilatation of the parasympathectomized and eserinized pupil. This is shown by pupil changes during metrazol convulsions (Fig. 5). The left eye, which can dilate only by means of sympathetic impulses, increases its diameter to 8 mm., whereas the normal eye dilates maximally, to 13 mm. The rapidity of the changes in both pupils and the quick return to the original diameters makes it highly

improbable that adrenin plays any rôle in these reactions. The second pupillary dilatation (Fig. 5) indicates a second but weaker sympathetic discharge.

In another animal, the left pupil was parasympathectomized and eserinized and the right one sympathectomized. The pupillary dilatation of the left eye during metrazol convulsions was again from 2 to 8 mm., but the sympathectomized pupil dilated only to 7.5 mm. instead of to 13 mm. as did the normal one* (Fig. 6).

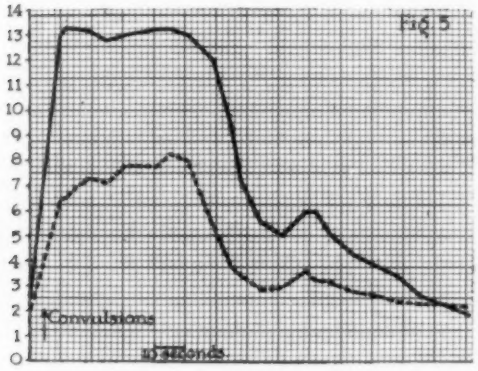


FIG. 5. Cat; no narcosis. Convulsions induced by 70 mg. metrazol intraperitoneally.

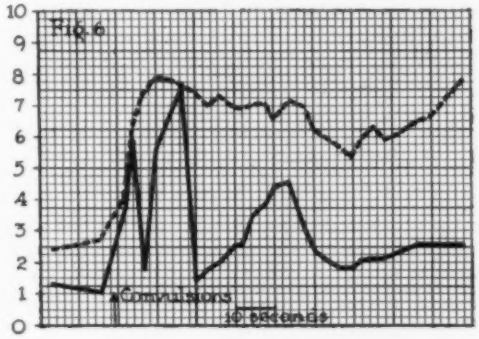


FIG. 6. Cat. ——— right eye; right cervical sympathetic cut. - - - - - - - left eye; left third nerve cut; local application of 1 per cent eserine to left eye. Metrazol convulsions after 80 mg. metrazol intraperitoneally.

These experiments support two conclusions: (i) The difference in pupillary dilatation between the normal and the sympathectomized pupil, in response to stimulation of afferent nerves, is largely due to the tonic action of the sympathetic; (ii) Reflex excitation of the sympathetic plays at most an insignificant rôle.

DISCUSSION

The pupillary dilatation following the stimulation of afferent nerves involves one or several of the following mechanisms: (i) Humoral dilatation (adrenin), (ii) nervous dilatation by, (a) Inhibition of the third nerve nucleus, or (b) Excitation of the cervical sympathetic.

Humoral dilatation can hardly play a rôle in these experiments, since marked dilatation occurs in the normal eye in the absence of a reaction in the parasympathectomized eye, while any humoral effect would be bilateral. Some of the stimuli employed were strong enough to elicit a humoral dilatation of pupils sensitized by previous removal of the superior cervical gan-

* It is interesting to note that the right eye in Fig. 6, which can alter its diameter only by varying the parasympathetic tone, shows, in addition to dilatation (parasympathetic inhibition), brief periods of pupillary constriction (parasympathetic excitation), whereas the left eye shows a continuous sympathetic discharge (cf. Gellhorn and Darrow, 1939).

glion, as shown in other experiments. Moreover, Gellhorn and Darrow (1939) found, in confirmation of the earlier work of McDowall (1925) and Bain, Irving and McSwiney (1935), that removal of the adrenals did not essentially alter the pupillary responses.

The older results in an extensive literature on reflex stimulation of the pupils are frequently difficult to evaluate because quantitative data concerning the mode of stimulation are omitted. The discrepancy between the experiments of Schiff (1875), who reported sensory stimulation without effect on the pupil after sectioning either of the spinal cord or of the cervical sympathetic, and those of Vulpian (1874) and Tuwim (1881), who observed pupillary dilatation after sectioning the cervical sympathetic or removing the superior ganglion, is hard to explain. The majority of investigators seem to agree with Vulpian and Tuwim rather than with Schiff and support the view that the reflex pupillary response is largely due to inhibition of the parasympathetic. Bechterew (1883), particularly, showed that the division of the brain stem behind the superior colliculi eliminates reflex dilatation of the pupil, although the light reflex remains intact, and concluded that pain causes a reflex inhibition of the third nerve center. His observations in man support this interpretation, for in man pain causes reflex dilatation only if the pupils are narrow and then they dilate only to the diameter they would possess in dim light. Braunstein (1894) reports numerous experiments, with quantitative measurements of the pupils, which show that sensory stimulation leads to pupillary dilatation after elimination of the cervical sympathetic but not after severing the spinal cord above the ciliospinal center. Similar results follow stimulation of afferent fibers in the splanchnic, confirmed recently by McDowall (1925), Byrne (1933), and Bain, Irving and McSwiney (1935).

The results of Lieben and Kahn (1930) fit into this interpretation, though the authors assume, without evidence, the additional involvement of a sympathetic center on the floor of the fourth ventricle. However, Chen, Lim, Wang and Yi (1936) showed that stimulation of the "sympathetic" pressor area at the bottom of the fourth ventricle produces, in addition to various sympathetic effects, a dilatation in a sympathectomized pupil only minimally different from that in the normal.

Karplus and Kreidl (1912, 1918) recognized the importance of inhibition of the third nerve in reflex dilatation of the pupil, but attributed considerable importance also to the sympathetic centers. This proof, however, is by no means convincing. They report (1911) one experiment without objective record, with the third nerve cut on the right side and the cervical sympathetic on the left, in which sciatic stimulation produced a moderate dilatation of the parasympathetomized pupil. In view of the observation of ourselves and of v. Brücke (1931) that the parasympathectomized pupil is about maximally dilated,* this statement appears to be erroneous. The later ob-

* v. Brücke found the diameter varied between 12 and 13 mm. in the cat!

servations of Karplus and Kreidl (1918), that section of the upper cervical cord abolishes pupillary dilatation in response to stimulation of the sciatic or of the branchial plexus but not to stimulation of the trigeminus, require a different interpretation. It seems highly probable that the same mechanism underlies the pupillary dilatation in all these experiments, and Karplus and Kreidl themselves interpret the effect of the stimulation of the fifth nerve as an inhibition of the third nerve center.

We, therefore, conclude, from a study of the literature and from our own observations, that pain stimuli elicit a dilatation of the pupil mainly by inhibiting the center of the third nerve. With excessive stimuli a small sympathetic discharge may also occur. A few discordant observations in the literature seem to be due to special conditions.

Anderson (1904) noted a pupillary dilatation in the parasympathectomized eye not only after stimulation of the sciatic but also after stroking the skin. We have been unable to confirm this and believe that Anderson, by deep chloroform narcosis, functionally eliminated all higher centers and created (by disinhibition) a state of heightened excitability of the ciliospinal center. This is further suggested by the presence of hippus. Foerster (1936, p. 227) noted an analogous reaction in patients with complete lesions of the cervical cord, in whom passive lifting of the paralyzed arm produced a maximal dilatation of the pupil.

If this interpretation is correct, it is to be expected that pharmacological agents, by heightening the excitability of the ciliospinal center, might bring about a sympathetic reflex dilatation, although this is absent under normal conditions. This seems to be proven by the experiments with metrazol here reported. They show a striking analogy to observations of Luchsinger (1880) and Guillebeau and Luchsinger (1882) who found, in contradistinction to the literature cited earlier, that spinal cord section did not interfere with the reflex dilatation while section of the cervical sympathetic abolished it. Such effects were only obtained, however, when the excitability of the ciliospinal center had been heightened by cocaine, picrotoxin, or strychnine. It is therefore, not permissible to infer from experiments carried out under such conditions that the normal reflex dilatation of the pupil involves the cervical sympathetic. What paths are involved in emotional excitement remains to be seen. The study by Dechaume (1937) of a dog whose thoracic and abdominal spinal cord had been removed seemed to indicate that emotional dilatation is linked up with the integrity of the ciliospinal center.

The slightly greater diameter of the normal than of the sympathectomized pupil* on reflex stimulation is probably due to the tonic action of the sympathetic, which becomes more pronounced as inhibition diminishes the parasympathetic tone. This interpretation seems to agree with that of v. Brücke (1931).

Since the sympathetic pupillary response to pain is ordinarily slight or

* The difference is ordinarily about 1 to 2 mm.

completely absent, the physiological significance of the sympathetic pupillary fibres must be discussed briefly. Experimental and clinical observations showing a decreased pupillary diameter after elimination of the cervical sympathetic indicate its tonic action. Alteration of this tonic function by pain occurs only when excessive stimuli are used or when a state of increased excitability has been induced in the central nervous system, and particularly in its sympathetic division. But the tonic activity may vary within wide limits, dependent on the intensity of the light reflex, for Gullberg, Olmsted and Wagman (1938) found that the sympathetic dilator tonus increases with increasing dark adaptation.

Under the conditions of reflex stimulation, however, the sympathetic tone of the pupillary fibers remains unchanged, though other sympathetic fibers in the cervical sympathetic may be excited. The contraction of the nictitating membrane, which regularly accompanies pupillary dilatation, is sufficient proof of sympathetic excitation; but this may occur when the normal and sympathectomized pupils dilate to the same extent, *i.e.*, when there is not the slightest indication of an alteration in sympathetic tone in the pupillary fibers.

Conclusions

The rôle of parasympathetic inhibition and that of sympathetic excitation in reflex pupillary dilatation in cats was analyzed by recording the pupillary changes in the normal, the parasympathectomized, and in the sympathectomized eye. It is shown that:

1. After section of the third nerve and local application of eserine, the threshold of the cephalad end of the cervical sympathetic remains unchanged; indicating that such a pupil may be used as an indicator of sympathetic impulses.

2. On reflex stimulation which evokes struggle and vocalization the parasympathectomized pupil remains unchanged or shows a very slight dilatation (not more than 1 mm.), whereas the normal pupil may dilate 7 mm.

3. After sensitization with metrazol the sympathetic reflex response of the pupil increases.

4. During metrazol convulsions the parasympathectomized and eserinized pupil dilates to 7 or 8 mm.

It is concluded that under normal conditions the pupillary dilatation in response to pain is almost exclusively due to parasympathetic inhibition but that under conditions which increase the excitability of the ciliospinal center, sympathetic discharges may contribute materially to the dilatation.

REFERENCES

Anderson, H. K. Reflex pupil dilatation by way of the cervical sympathetic nerve. *J. Physiol.*, 1904, *30:* 15–24.

Bain, W. A., Irving, J. T., and McSwiney, B. A. The afferent fibres from the abdomen in the splanchnic nerves. *J. Physiol.*, 1935, *84:* 323–333.

Bechterew, A. Über den Verlauf der die Pupille verengernden Nervenfasern im Gehirn und über die Localisation eines Centrums für die Iris und Contraction der Augenmuskeln. *Pflüg. Arch. ges. Physiol.*, 1883, *31:* 60–87.

BRAUNSTEIN, PH. C. *Zur Lehre von der Innervation der Pupillenbewegung.* Wiesbaden, 1874.

BYRNE, J. G. *Studies on the physiology of the eye.* London, 1933, 240 pp.

CHEN, M. P., LIM, R. K. S., WANG, S. C., and YI, C. L. On the question of a myelon-cephalic sympathetic centre, III. *Chin. J. Physiol.*, 1937, *11:* 367–407.

CLAES, E. Activités pupillo-motrices du diencéphale et du mésencéphale. *C. R. Soc. Biol., Paris*, 1936, *123*, 1009–1013.

DECHAUME, J. Les chiens sans moelle du Pr. Hermann. *Rev. neurol.*, 1937, *68:* 409–435.

FOERSTER, O *Handbuch der Neurologie.* Vol. 5, 1936, Berlin (J. Springer).

GELLHORN, E., and DARROW, C. W. The effect of metrazol on the autonomic nervous system. (In press.)

GUILLEBEAU, A., and LUCHSINGER, B. Zur Existenz des Centrum cilio-spinale inf. von Budge. *Pflüg. Arch., ges. Physiol.*, 1882, *28:* 72–74.

GULLBERG, J. E., OLMSTEAD, J. M. D., and WAGMAN, I. H. Reciprocal innervation of sphincter and dilator pupillae. *Amer. J. Physiol.*, 1938, *122:* 160–166a.

INGRAM, W. R., RANSON, S. W., and HANNETT, F. I., Pupillary dilatation produced by direct stimulation of the tegmentum of the brain stem. *Amer. J. Physiol.*, 1931, *98:* 687–691.

KARPLUS, J. P., and KREIDL, A. Gehirn und Sympathicus. Sympathicusleitung im Gehirn und Halsmark. *Pflüg. Arch. ges. Physiol.*, 1912, *143*, 109–127; and 1918, *171:* 192–200.

LIEBEN, S., and KAHN, R. H. Die emotionelle Reaktion der Pupille. *Pflüg. Arch. ges. Physiol.*, 1930, *225:* 699–704.

LUCHSINGER, B. Weitere Versuche und Betrachtungen zur Lehre von den Rückenmarks-zentren. *Pflüg. Arch. ges. Physiol.*, 1880, *22:* 158–168.

MCDOWALL, R. J. S. The reactions of the pupil in the chloralosed animal. *Quart. J. Physiol.*, 1925, *15:* 177–180.

SCHIFF, M. *La pupille considéré comme esthésiomètre.* Paris, 1875.

TUWIM, J. Über die physiologische Beziehung des Ganglion cervicale supremum zu der Iris und den Kopfarterien, *Pflüg. Arch. ges. Physiol.*, 1881, *24:* 115–134.

URY, B., and GELLHORN, E. Influence of oxygen deficiency on reflex dilatation of the pupil. *Proc. Soc. exp. Biol. N.Y.*, 1938, *38:* 426–427.

v. BRÜCKE, H. Recovery of normal tonus in the course of regeneration of the cervical sympathetic nerve. *J. comp. Neurol.*, 1931, *53:* 225–261.

VULPIAN, A. Note relative a l'influence de l'extirpation du ganglion cervical superieur sur les movements de l'iris, norm. et path. *Arch. Physiol.*, 1874, *1:* 177. [Quoted from Vulpian, C. R. 1878, *86*, 1436–1437. "Expérience démontrant que les fibres nerveux, dont l'excitation provoque la dilatation de la pupille, ne proviennent pas toutes du cordon cervical du grand sympathique."]

EFFECTS OF HYPOGLYCEMIA AND PENTOBARBITAL SODIUM ON ELECTRICAL ACTIVITY OF CEREBRAL CORTEX AND HYPOTHALAMUS (DOGS)*

HUDSON HOAGLAND, HAROLD E. HIMWICH, ELDRIDGE CAMPBELL, JOSEPH F. FAZEKAS AND ZAREH HADIDIAN

The Biological Laboratories, Clark University, Worcester, Mass., and The Departments of Physiology and Pharmacology, and Surgery Albany Medical College, Albany, New York

(Received for publication February 24, 1939)

A CONSPICUOUS property of most normal human electroencephalograms is the presence of regular sinusoidal alpha waves or "10-per-second" waves, that may best be recorded from the resting subject with closed eyes. Hoagland and his collaborators have demonstrated that the *relative frequency* of these waves, *other things being equal*, is proportional to the rate of respiration of the cortical cells producing the waves. Changes of frequency produced by temperature via diathermy (Hoagland, 1936a, 1936b) give definite energies of activation or temperature characteristics identical with the principal modal values for oxygen consumption and CO_2 production of numerous tissues *in vitro*. This, from the nature of the equation used, could only occur if frequency were proportional to respiration rate. Dinitrophenol accelerates alpha frequencies along a smooth curve (Hoagland, Rubin and Cameron, 1939) and thyroxin also accelerates the frequencies along with the B.M.R. (Rubin, Cohen and Hoagland, 1937). Reduction of blood sugar by insulin causes the alpha waves to slow, after a lag, with the falling sugar and later to return when glucose is given (Hoagland, Rubin and Cameron, 1937). Himwich *et al.* (1939) have confirmed this last finding and demonstrated a relation between oxygen consumption of the brain and alpha wave frequency.[1] Sugar is probably the chief brain fuel (Himwich and Nahum, 1932).

These findings are not, of course, to be interpreted as meaning that the *only* modifiers of brain wave frequencies are necessarily changes in cell respiration. Afferent stimulation, which modifies frequencies, may do so by locally changing cell respiration or by modifying the electrical constants (impedance) of the cells or their connections through permeability changes. Absolute differences in frequencies of different cell groups also are not to be regarded as due to corresponding absolute differences in rate of O_2 consumption, but rather to differences in structure of the cell walls or connecting fibers. These considerations in no way militate against the view that certain *relative* frequency changes under standard conditions are due to changes in rates of cell metabolism. The waves may be regarded as "spontaneous" in

* This investigation was aided by a grant from Child Neurology Research (The Friedsam Foundation).

[1] These rate considerations apply only to frequencies which have the dimensions of rates, *i.e.*, reciprocal times. Amplitude and total energy are not rates and their relation to metabolism should not be confused with the frequency factor.

origin, or due to closed or "reverberating" circuits set off initially by afferent stimuli. In either mechanism a type of relaxation oscillator system discussed by Hoagland (1936b) is equally consistent with the experimental findings. In the latter case oxidative recovery from the refractory state of the circuit may be pictured as determining the frequency.

Page (1937) in a review has written, "Important results of Quastel and Wheatley, and Davis and Quastel seem to show that all narcotic drugs (including the barbiturates) have one property in common: they inhibit specifically at low concentration the oxidation by brain of substances essential to the metabolism of carbohydrates such as glucose, lactic acid and pyruvic acid. . . . Their results suggest that narcotics do not interfere with access of oxygen to brain cells or with activation of oxygen by brain catalysts, but with the mechanisms that result in activation of lactic acid and pyruvic acid."

An anesthetic like pentobarbitol sodium (nembutal), on the basis of this *in vitro* work with brain slices, might give typical brain wave changes characteristic of reduced brain respiration. As in hypoglycemia, where respiration is slowed by removing the brain's fuel supply, so we might expect that nembutal would (i) slow primary or "alpha" frequencies and (ii) as in hypoglycemia, delta waves (all waves longer than the basic alpha waves) might become more pronounced. Deprivation of O_2 by N_2 breathing in man in extremes of deprivation slows the alpha frequency and, in lesser degrees of deprivation, increases the random slow wave activity (Gibbs, Davis and Lennox, 1935). Variations in pH due to CO_2 changes produce in themselves modifications. Increase in CO_2 enhances short wave components (Lennox, Gibbs and Gibbs, 1936). These are complicating factors in considering alpha frequencies directly in relation to oxygen tension. But the evidence, from the temperature analysis, that cell respiration is a basic determinant of frequency is not subject to criticism on pH grounds. The energies of activation for alpha frequencies not only agree with the principal modal values for cellular respiration, but Hadidian and Hoagland (unpublished) have been able to show that two of the three values correspond to specific respiratory enzyme systems which, under the conditions of the experiments, act as chemical pacemakers for the cortical respiration. Sizer (1937) has shown that pH variations over a wide range (3.2–7.9) have no effect on activation energies of certain specific enzymes.

Prawdicz-Neminski (1925) showed that the dog cortex displays a basic predominant rhythm of 11 to 16 per sec. along with a secondary rhythm of 20 to 32 per sec. In general we have confirmed his findings. In 18 dogs we have found (i) a basic rhythm presumably corresponding to the alpha rhythm of man ranging from 14 to 18 per sec. in dogs without anesthetic from widely varied parts of the cortical dura, along with faster rhythms of lesser amplitude. The present investigation presents certain information concerning the relative effects of nembutal and of hypoglycemia on the electrical activity of the cerebral cortex and the hypothalamus.

PROCEDURE

Our records have been taken with either a one-channel magnetic ink-writer recording on paper tape (built by Garceau) or a two-channel matched amplifier system also recording with pens (built by Grass). We have used throughout monopolar (grid to ground) recording which has been demonstrated to give better local representation than bipolar recording (Rubin, 1938). The leads were either chlorided silver wires or small pointed solder tips attached to copper wires insulated to 1 mm. or so of the tip. In general a day before the time of observation the dogs were anesthetized with nembutal (0.7 cc. of 5 per cent solution per kg. body weight). The hypothalamus was then exposed surgically under sterile conditions, using the subtemporal route, and leads were inserted. One input grid lead was placed in the region of the mammillary bodies, a second in the region immediately above the optic chiasm and a third on the cortex. A fourth "indifferent" lead was inserted under the scalp behind the homolateral ear. By the next day the dogs were able to walk about and appeared to be well recovered from operation and anesthesia. Four of the 18 dogs were studied as acute preparations under nembutal anesthesia with only the cerebral cortex exposed.

In the figures we refer to responses from "mammillary bodies" and "supraoptic nucleus." It is understood that these structures were located by landmarks at the time of operative exposure and were always checked post mortem, although brain sections were not made. It might thus be more correct to refer to "mammillary body region" and "supraoptic nucleus region."

RESULTS

Figure 1A shows electrical responses from a dog (cortex only) anesthetized with nembutal. At 9:25 the record consists of large delta waves and of a basic rhythm of 10 per sec. This rhythm may be seen to speed up during the day as the anesthetic wears off and, with this increase in "alpha" frequency, there is a decrease in delta wave activity, until at 2:15, when the dog is fully recovered, there is a clear basic "alpha" rhythm of 18 per sec. A second dose of nembutal reëstablishes the earlier condition. The parallelism between the nembutal effect on brain waves and that of hypoglycemia in man is indeed striking (see Hoagland, Rubin and Cameron, 1937), and is what would be expected if the changes in both cases were due to inhibitory action on the respiration of the cortical cells.

Figure 1B shows responses from the unanesthetized cortex of a dog on successive days corresponding to different blood sugar levels. The basic rhythm is reduced from 15 to 8 on the second day with reduced blood sugar and the delta waves are enhanced. This picture is the same as that encountered in the human E.E.G. following reduction of blood sugar by insulin as originally described by Hoagland, Cameron and Rubin (1936, 1937) and confirmed by Yeager and Baldes (1937) and by Himwich *et al.* (1939). Since nembutal and hypoglycemia both affect the electrogram in much the same way, it is obvious that nothing quantitative can be said about changes due to either factor alone in studies of insulin shock which involves the use of nembutal anesthesia.

Figure 1C shows simultaneously recorded responses from anterior hypothalamus and cortex before anesthesia on the day after operation and again 20 min. after an anesthetizing injection of nembutal. The basic cortical ("alpha") rhythm is slowed from 17 to 9, and, as also in Fig. 1A, the amplitude is increased (cf. Derbyshire, Rempel, Forbes and Lambert, 1936). No significant effect is seen upon the hypothalamic lead. This was typical in all

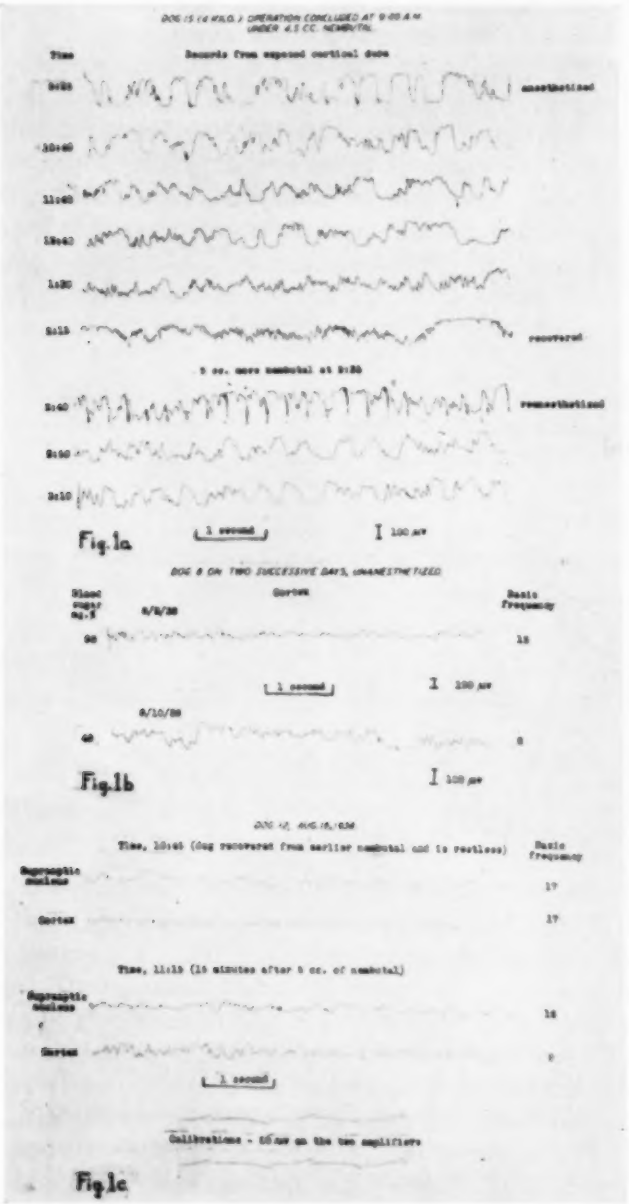


FIG. 1. A. Sample records showing effect of nembutal anesthesia on the dog cortex. The dog is fully recovered from its first dose by 2:15. Note the decrease in delta waves and increase in the basic "alpha" frequency with recovery. Note also the spike and wave formations following the second dose. Negativity is up throughout.

B. Effect on "alpha" rhythms of two blood sugar levels. This dog was operated on Aug. 8, 1938.

C. Two pairs of simultaneous records showing effect of nembutal on cortical waves and lack of effect on waves from the anterior hypothalamus. Dog operated on Aug. 15, 1938.

14 dogs. Surgical anesthesia with nembutal has no effect on the electrogram from either anterior or posterior hypothalamus.

Grinker (1937) described an ingenious method of recording from the hypothalamic region by embedding a grid lead in the bone in the roof of the pharynx below the hypothalamus. His method is applicable not only to common laboratory mammals but also to man. Hoagland, Cameron, Rubin, and Tegelberg (1938), using Grinker's method, have made studies in man of simultaneously recorded cortical potentials and potentials from a lead in the pharyngeal roof near the hypothalamus. Asynchronous alpha waves were found at both leads and, following emotionally charged remarks and queries, delta waves were obtained at both leads. A month later, and quite inde-

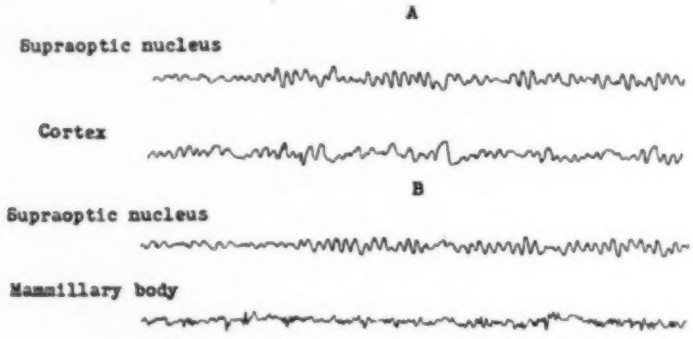


FIG. 2. Two pairs of records from an unanesthetized dog. A. Upper, from anterior hypothalamus; lower, from cortex (simultaneous recording).

B. Upper, from anterior hypothalamus; lower, from mammillary body (simultaneous recording). The basic rhythms are 14 per sec.

pendently, Grinker and Serota (1938) reported this same result. Hoagland, Cameron and Rubin showed that the hypothalamic delta waves on the average precede the corresponding cortical deltas by approximately 4 msec., suggesting detonation of the cortex by way of the hypothalamus following emotional stimulation. In view of this it was desirable to compare responses obtained directly from the anterior hypothalamus in unanesthetized animals with those obtained by the Grinker technic in which the hypothalamic lead is embedded in the bone. An especially clear-cut record of this sort on an unanesthetized dog is shown in Fig. 2. Simultaneously recorded, 14 per sec. nonsynchronous, basic or "alpha" rhythms are seen from cortex and anterior hypothalamus which are like those obtained by the Grinker technic in man (cf. figures in Hoagland, Cameron, Rubin and Tegelberg, 1938 and Grinker and Serota, 1938). The posterior hypothalamic lead in the mammillary body region of this dog, though only about 1 cm. distant, shows an entirely independent and faster rhythm, thus confirming the localizing efficacy of our method of monopolar recording.

Figure 3 demonstrates the changes in activity of cortex and anterior and posterior hypothalamus during insulin shock in a dog initially anesthe-

tized with nembutal. Since from 10:05 to 2:30 the nembutal effect is wearing off while the hypoglycemic effect is coming on, we should expect the cortical picture to be relatively constant since hypoglycemia and nembutal both slow "alpha" waves and enhance delta wave activity (Fig. 1). This is seen to be the case. By 2:30 may be seen the typical picture of hypoglycemia familiar in man for a corresponding blood sugar level. There is at this time comparatively little hypothalamic change. By 5:00 the cortical activity is

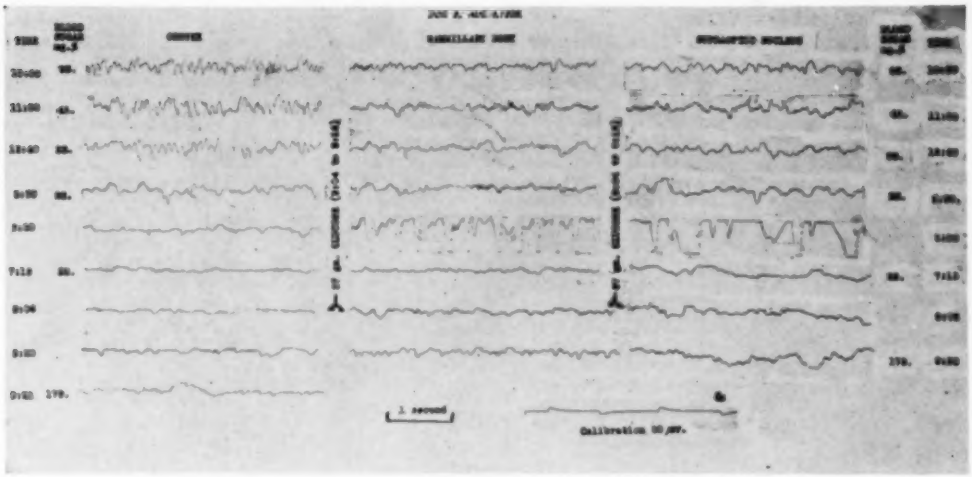


FIG. 3. Records from cortex, posterior hypothalamus, and anterior hypothalamus during insulin shock and recovery. At each recorded time successive records were made from the three regions about one minute apart. The dog was given nembutal at 9:10 and again at 11:50. The frequency changes in "alpha" waves cannot, therefore, be related to sugar changes alone. Note augmentation of cortical delta waves at 2:30 and flattening of record by 7:15. Note slowness of return of cortical activity after administering sugar. The hypothalamic responses are much less depressed and return more rapidly after sugar injection (see records of 9:06 and 9:20). Note the violent responses of the hypothalamus at 5:00, producing amplifier block. These surges were not accompanied by convulsions nor were they associated with pulse or respiration. Operation on Aug. 8, 1938.

greatly reduced but there are violent surges of activity at the hypothalamic lead. The blood sugar had been 45 mg. per cent or less for 6 hours. By 7:15 the cortex is silent but there are still regular rhythms from the hypothalamus, especially from the mammillary body. After injection of glucose at 9:04 the amplitude of hypothalamic waves increases rapidly, the cortical response remaining feeble and irregular. This result is typical of 5 experiments on as many dogs.

Figure 4 shows the great stability of the hypothalamus during insulin shock. The blood sugar ranged around 35 mg. per cent for 5.5 hours but the basic rhythms at the two hypothalamic leads, simultaneously recorded, are unaffected. The regular large deflections especially in evidence at 4:30 from the mammillary body are believed to be electrode artefacts.

Figure 5 shows clearly the early failure of the cortex with pronounced

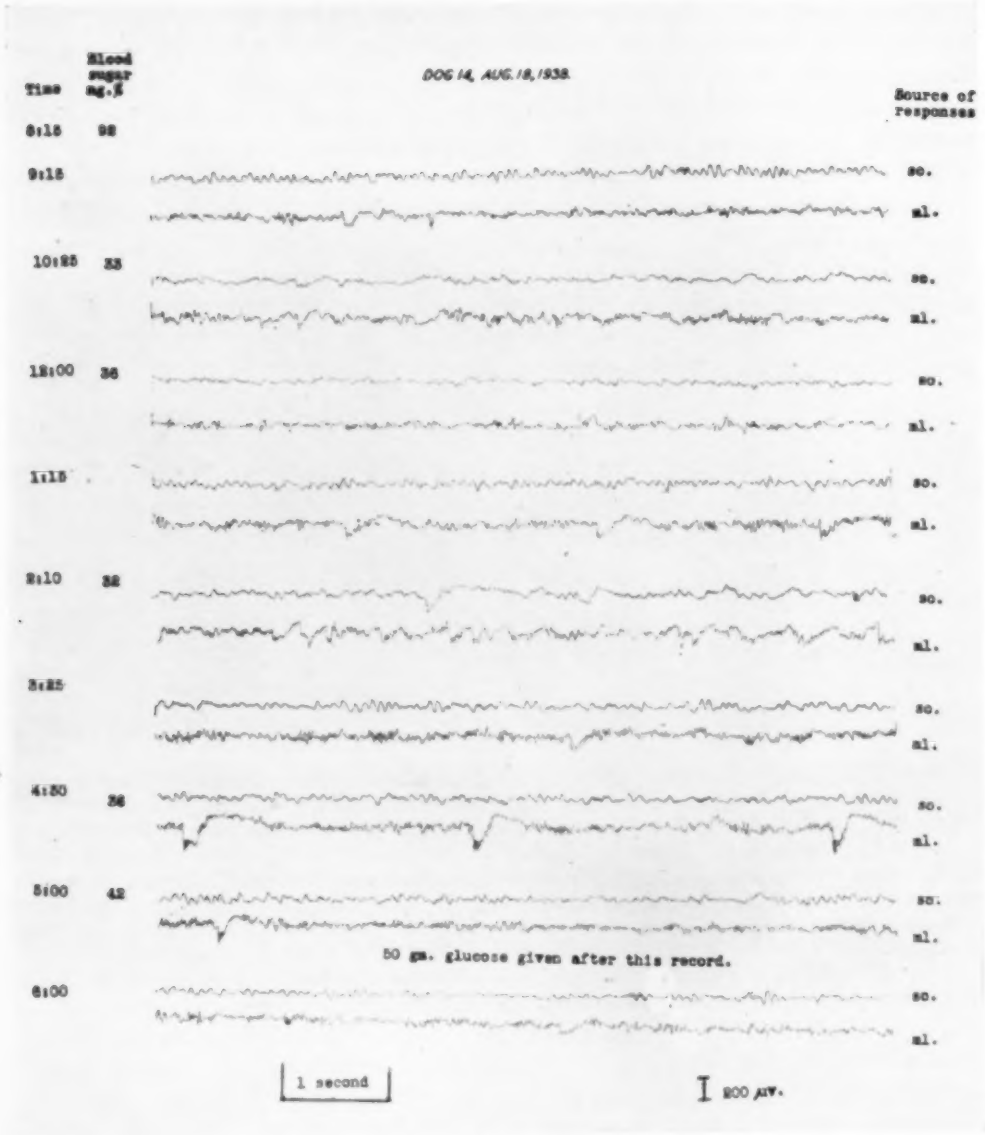


FIG. 4. Simultaneously recorded pairs of electrograms taken from the region of the supraoptic nucleus (so.) and from the region of the mammillary body (ml.) during the lowering of blood sugar by insulin. 20 U. insulin were given repeatedly at 8:15, 10:15, 12:10, 2:35, and 4:35. The first record at 9:15 is prior to anesthesia (the dog was operated on the day before). 4 cc. nembutal were given at 10:15. At 5:35 glucose (50 gm.) was given. Note the great stability of responses from the hypothalamus. Despite anesthesia and blood sugar changes the activity of this center is essentially unmodified.

hypoglycemia in an anesthetized dog, along with the relative stability of the hypothalamic activity. At 5:55 the record shows a uniform rhythm from the hypothalamus which in 3 animals we observed very late in hypoglycemic

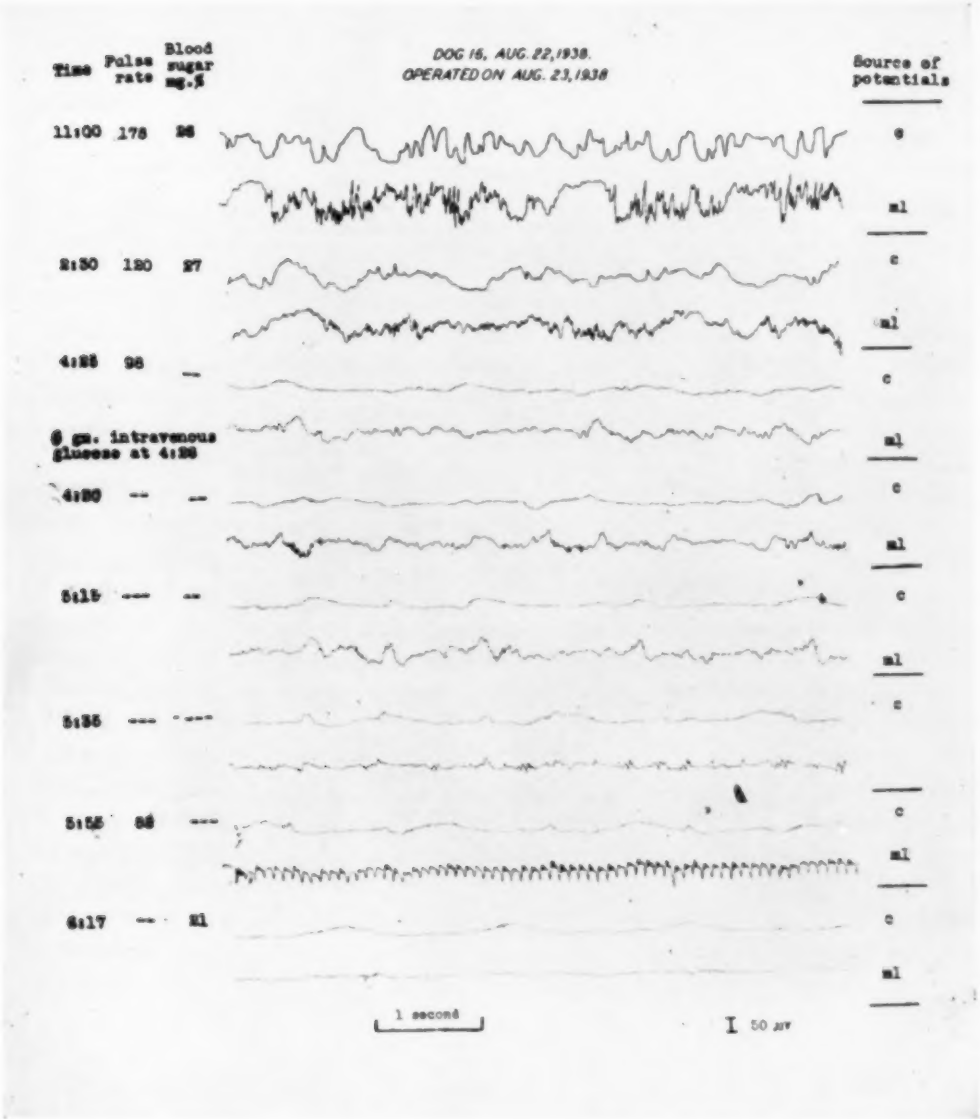


FIG. 5. Showing the effect of prolonged insulin hypoglycemia on simultaneously recorded oscillograms from the cortex (c.) and from the mammillary body region of the hypothalamus (ml.). For seven hours the blood sugar analyses are not >27 mg. per cent. A small amount of glucose at 4:28 has little if any restorative action. Note failure of cortex and relative stability of hypothalamic activity, and also progressive fall in pulse rate. Note the rhythms from the hypothalamus at 5:55 prior to complete failure of activity at the two leads. These rhythms did not correspond to pulse or to respiration or to any detected movement of the animal. At 6:20 the brain was frozen and found to contain only 14/100 gm. of glycogen.

shock. Because of restlessness and hypoglycemic convulsions producing artefacts and endangering the electrodes, we used anesthesia (nembutal) in

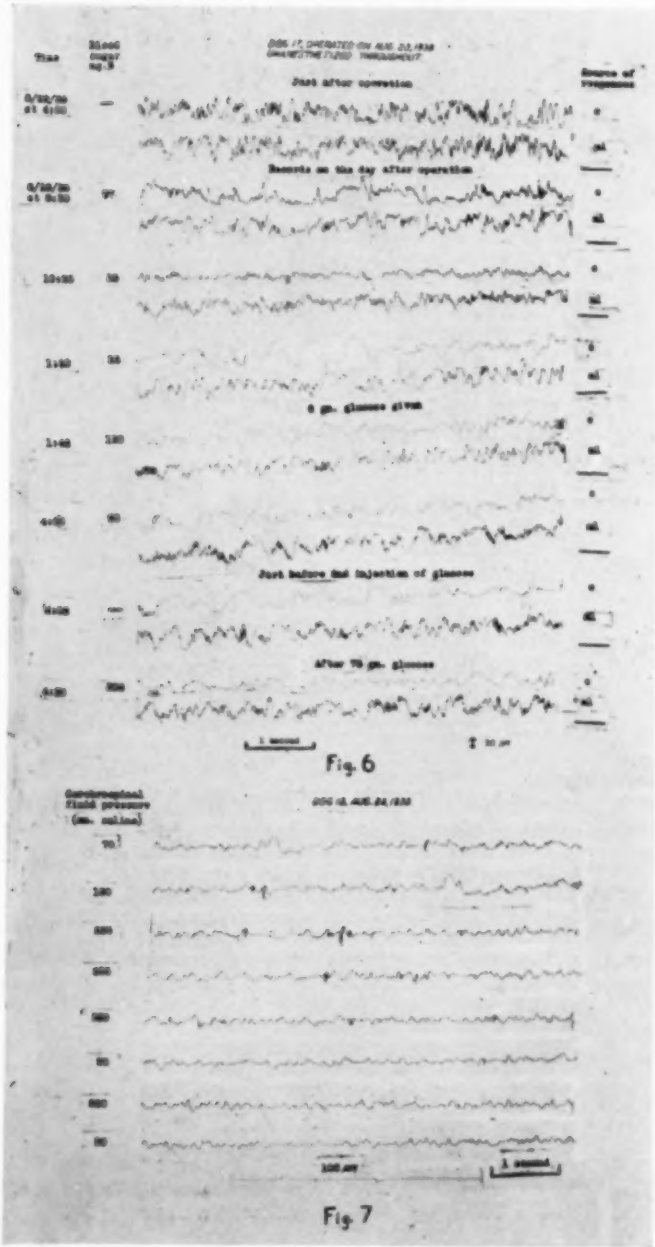


Fig. 6

Fig. 7

FIG. 6. Records from an unanesthetized dog showing cortical (c) responses and responses from the mammillary body region of the hypothalamus during insulin hypoglycemia and recovery. Sugar was given between the 1:40 and 1:46 records, followed again by insulin. Sugar was again given after the 4:08 record. The blood sugars in this experiment remained comparatively high. This particular dog, like some persons, showed irregular waves difficult to quantify.

FIG. 7. The cerebrospinal fluid pressure was changed by running saline in and out of the cisterna magna. No correlating modifications of the cortical electrogram recorded through the dura were seen. Nembutal anesthesia.

nearly all our insulin experiments. One of our dogs was, however, of so quiet a temperament that we were able to experiment post-operatively without using anesthesia. Unfortunately, this dog, like some persons, did not have a very clear "alpha" rhythm and showed considerable delta wave activity. Figure 6 shows results of this experiment. The blood sugar was not reduced below 55 mg. per cent and the corresponding small changes in cortical activity and lack of changes in hypothalamic activity are of the sort to be anticipated from the above discussion and also from the work with man.

Marked hypoglycemia raises the intracranial pressure about 50 per cent (see Gellhorn, 1938) and it was possible that some of the electroencephalographic changes accompanying hypoglycemia might be due to hydrostatic pressure effects. Walter (1938) in a review notes that with the elevation of intracranial pressure resulting from such agencies as ventricular obstruction, concussion, meningitis and cerebral tumor that delta waves at about 3 per sec. occur over the entire cortex. But no correlation has been found between actual cerebrospinal fluid pressure and the slow waves. Rather, the delta waves seemed to be associated with the extent of cortical impairment of function. He reported, however, that the generalized delta activity could be reduced by intravenous injections of hypertonic solutions but it was little affected by the removal of cerebrospinal fluid. Walter has described cases of cerebral oedema with no measurable pressure changes which showed the slow discharge. The oedema seemed to be the important factor rather than the hydrostatic pressure.

To test the effect of hydrostatic pressure *per se*, we inserted into the cisterna magna a hypodermic needle which was held rigidly fastened to a nail parallel to the needle and driven into the occipital bone just above the foramen magnum. Various heads of hydrostatic pressure (saline solution) were then applied from a reservoir and measured on a manometer. Figure 7 shows the results. It is clear that a 16-fold variation in pressure in itself produces no effect whatever on the cortical electrogram of the dog, at least during the hour or so consumed by the experiment.

Discussion

These results with dogs confirm and extend the findings of Hoagland, Rubin and Cameron concerning hypoglycemia and the electroencephalogram in man. Along with the nembutal effects they add further evidence in favor of the view that the relative *frequency* of cortical rhythms is determined basically by the respiratory rate of the cortical cells.

Dubner (1938) in a preliminary abstract reports studies of the electrical activity from the lateral geniculate body of cats under nembutal anesthesia. He writes, "Insulin (up to 15 units per kgm. subcutaneously) did not give gross convulsions, though potential changes were definite within an hour. The small high-frequency potentials superposed on the usual optic rhythm were accelerated and intensified; and the normal 'on' response to light was replaced by a series of 3 to 5 large oscillations, mainly positive, and followed

by a prolonged high frequency after discharge. . . . The normal picture was restored within five minutes after intravenous injection of glucose." These results showing an increase in fast wave components with hypoglycemia appear to be at variance with our findings with dogs and with the results obtained with man. Different animals and different centers were involved in Dubner's experiments as compared to ours. Also, one is led to wonder if the high frequency components may not be new superimposed rhythms, and not progressive *frequency* accelerations in the same rhythm. Further, nothing is said concerning modifications of the frequency of the basic optic rhythm. If the nembutal effect were wearing off as the hypoglycemic effect were coming on we would expect that the basic optic rhythm to which he refers would remain unchanged as in our Fig. 3 for reasons already pointed out. A more extended discussion of this matter would not appear to be profitable until Dubner's results are published.

Sugar and Gerard (1938) have shown that following sudden occlusion of the circulation that the "highest" and phylogenetically newest centers fail in electrical activity first and regain activity last when the circulation is restored. Their records were made on anesthetized cats, using the Horsley-Clark technic, but did not include the hypothalamus. Following occlusion they found, in general, that centers were first briefly stimulated to hyperactivity, followed by a decrease in both amplitude and frequency of the waves. Our results showing greater resistance to hypoglycemia and nembutal of the hypothalamus in contrast to the cortex are similar to their findings on the susceptibility of new and older centers to oxygen deprivation.

We find that only in very late stages of prolonged hypoglycemia in dogs does hyperactivity of the hypothalamus occur (Fig. 3 and 5). This hyperactivity is manifested only a long time after cortical failure occurs, an advanced condition which in human insulin treatments does not take place. Hyperactivity of the autonomic system, as judged by sweating, salivation, etc. in both man and dogs occurs much earlier, at a time when the cortical response shows either a greatly slowed or absent alpha rhythm along with prominent delta waves. In all of our experiments, the dog hypothalamic responses have at this time been quite unchanged. It seems probable from these findings that the relatively early external signs of sympathetic hyperactivity result from a reduction of cortical control over sympathetic motor mechanisms which permit more extensive motor manifestations for the *same* degree of hypothalamic discharge rather than from a direct stimulating action at this stage of hypoglycemia on the hypothalamus. Hyperactivity of this center does occur but only in late stages of prolonged hypoglycemia.

Our findings superficially appear to be at variance in one respect with a published figure from Grinker and Serota (1938) who show a slowing of the hypothalamic rhythm in the cat *immediately* following the injection of nembutal. This result may be due to one of several reasons (i) the cat and dog may differ in this respect, though this is unlikely, (ii) our experiments are

not exactly comparable since we have never recorded hypothalamic changes *immediately* after injecting nembutal but have made such comparisons only before and after an anesthetizing dose 20 min. or so following the injections, (iii) the dose used by Grinker and Serota was much greater than ours, since they superimposed on the original anesthetizing intraperitoneal dose 100 mg. of nembutal intravenously, an amount which by itself would be more than enough to anesthetize a two kilogram cat. With such an extreme depression of the c.n.s. we would expect hypothalamic activity to decrease as it does, for example, in the extremes of hypoglycemia. Our experiments indicate that as far as anesthetic amounts of nembutal are concerned, cortical activity is depressed, while hypothalamic activity seems unaffected.

Summary

1. Electrograms have been recorded from the dog cortex (18 dogs) and from anterior and posterior hypothalamus (14 dogs) both with and without anesthetic under varying conditions of insulin hypoglycemia.

2. The effect of hypoglycemia on the cortical activity is similar to that in man, the alpha rhythms are slowed and the delta waves increase in prominence. In more prolonged hypoglycemia the cortical responses fail completely and are restored only an hour or so after injection of glucose. Both posterior and anterior hypothalamus show much stability compared to the cortex. No changes are noted until some time after failure of electrical activity of the cortex when a short period of hyperactivity of the hypothalamic centers may develop, followed later by failure just before death. Injected glucose restores hypothalamic activity some time before that of the cortex.

3. Nembutal, which reduces cortical respiration *in vitro*, produces cortical changes similar to those of hypoglycemia except that it considerably enhances the amplitude of alpha waves at the same time that it slows their rhythm. In contrast to this, no differences were seen in hypothalamic rhythms before and after nembutal anesthesia.

4. Our results show independence of responses from cortex, from a region near the supraoptic nucleus, and from the mammillary body region. The latter two grid leads were approximately 1 cm. apart. The anterior hypothalamic response, recorded directly by our method, gives records indistinguishable from those obtained by the Grinker technic in which a grid lead is embedded in the bone at the roof of the pharynx.

5. Changes (as much as 16-fold) in hydrostatic pressure of the cerebrospinal fluid are *per se*, without effect on the cortical electrogram.

REFERENCES

Dubner, H. Further studies of factors influencing brain rhythms. *Amer. J. Physiol.*, 1938, *123:* 56–57.

Gellhorn, E. Effects of hypoglycemia and anoxia on the central nervous system. *Arch. Neurol. Psychiat., Chicago*, 1938, *40:* 125–146.

Grinker, R. R. A method for studying and influencing corticohypothalamic relations. *Science*, 1938, *87:* 73–74.

GRINKER, R. R., and SEROTA, H. Studies on corticohypothalamic relations in the cat and man. *J. Neurophysiol.*, 1938, *6:* 573–589.

HIMWICH, H. E., and NAHUM, L. H. The respiratory quotient of the brain. *Amer. J. Physiol.*, 1932, *101:* 446–453.

HIMWICH, H. E., HADIDIAN, Z., FAZEKAS, J. F., and HOAGLAND, H. Cerebral metabolism and electrical activity during insulin hypoglycemia in man. *Amer. J. Physiol.*, 1939, *125:* 578–585.

HOAGLAND, H. Pacemakers of human brain waves in normals and in general paretics. *Amer. J. Physiol.*, 1936a, *116:* 604–615.

HOAGLAND, H. Some pacemakers of rhythmic activity in the nervous system. *Cold Spr. Harb. Symp.*, 1936b, *4:* 267–284.

HOAGLAND, H., RUBIN, M. A., and CAMERON, D. E. Electrical brain waves in schizophrenics during insulin treatments. *J. Psychol., Provincetown*, 1936, *3:* 513–519.

HOAGLAND, H., RUBIN, M. A., and CAMERON, D. E. The electroencephalogram of schizophrenics during insulin hypoglycemia and recovery. *Amer. J. Physiol.*, 1937, *120:* 559–570.

HOAGLAND, H., RUBIN, M. A., CAMERON, D. E., and TEGELBERG, J. J. Emotion in man as tested by the delta index of the electroencephalogram: II. Simultaneous records from cortex and from a region near the hypothalamus. *J. gen. Psychol.*, 1938, *19:* 247–261.

HOAGLAND, H., RUBIN, M. A., and CAMERON, D. E. Brain wave frequencies and cellular metabolism. Effects of dinitrophenol. *J. Neurophysiol.*, 1939, *2:* 170–172.

LENNOX, W. G., GIBBS, F. A., and GIBBS, E. L. Effects on the electroencephalogram of drugs and conditions which influence seizures. *Arch. Neurol. Psychiat., Chicago*, 1936, *36:* 1236–1245.

PAGE, I. H. *Chemistry of the brain.* Charles C Thomas, Springfield, Ill., 1937, xvii, 444 pp.

PRAWDICZ-NEMINSKI, W. W. Zur Kenntnis der electrischen und der Innervationvorgänge in den funktionellen Elementen und Geweben des tierischen Organismus. Electrocerebrogramm der Säugetiere. *Pflüg. Arch. ges. Physiol.*, 1925, *209:* 363–382.

RUBIN, M. A., COHEN, L. H., and HOAGLAND, H. The effect of artificially raised metabolic rate on the electroencephalogram of schizophrenic patients. *Endocrinology*, 1937, *21:* 536–540.

SIZER, I. W. The kinetics of catalysed sugar hydrolysis as a function of temperature. *J. cell. comp. Physiol.*, 1937, *10:* 61–77.

SUGAR, O., and GERARD, R. W. Anoxia and brain potentials. *J. Neurophysiol.*, 1938, *6:* 558–572.

WALTER, W. G. Critical review: The technique and application of electroencephalography. *J. Neurol. Psychopath.*, 1938, *1:* 359–385.

YEAGER, C. L., and BALDES, E. J. The electroencephalogram in organic and inorganic mental disorders. *Proc. Mayo Clin.*, 1937, *12:* 705–711.

CORTICAL ACTION POTENTIALS DURING ANESTHESIA

H. K. BEECHER AND F. K. McDONOUGH
Surgical Laboratory, Massachusetts General Hospital and Department of Physiology, Harvard Medical School, Boston

(Received for publication March 3, 1939)

INVESTIGATION of the anesthesia process has been handicapped by lack of precisely measurable elements. The electrical activity of the central nervous system, and in particular that of the cerebral cortex, offers a measurable component which can be followed during anesthesia. With the rapid development of electrophysiology in recent years, new tools have been evolved which promise to be of great service in clarifying certain phases of the action of anesthetic agents. The use of the electroencephalogram as an approach to the study of anesthetic agents is not new,* but the usefulness of the results obtained has been limited by the fact that generally each observer has studied only one or two agents. Even when the same agents have been studied in several laboratories many other factors have varied, such as animals, position and type of electrodes, depth of anesthesia, and so on. It is impossible to consider these data from a comparative standpoint. The study of widely differing anesthetics under comparable conditions was begun by Derbyshire, Rempel, Forbes and Lambert (1936), who selected three agents as representative of three distinct classes and compared the electroencephalogram under them with that in unanesthetized animals both waking and sleeping. At the suggestion of Dr. Forbes this earlier study has been extended and a considerable number of anesthetic agents has been studied under both light and deep anesthesia, with the aim in view of getting more insight into the nature of the cortical action potentials, and with the hope that leads might be opened up which would throw light on the anesthesia process itself.

MATERIALS, APPARATUS AND METHODS

Animals. Cats were employed in all experiments. The right posterior sigmoid gyrus of the cortex was exposed, and activity recorded from the region of the sensory area in all cases.

Anesthetic agents. The seventeen compounds studied and the number of experiments under each follow: Nitrous oxide, 4; cyclopropane, 3; ether, 4; divinyl ether, 4; ethylene, 3; trichlorethylene, 3; ethyl alcohol, 3; ethyl chloride, 3; ethyl urethane, 3; chloroform, 5; amylene hydrate,** 3; tribromethanol,** 3; "evipal" (1-methyl-5-Δ' cyclohexenyl-5-methyl barbituric acid), 3; paraldehyde, 3; sodium barbital, 3; chloralosane†, 4; and "nembutal" (sodium ethyl (1-methyl-butyl)barbiturate), 3.

Levels of anesthesia. These were determined by the flexion reflex evoked by electrical stimulation of the central end of the cut left sciatic nerve. The stimulating electrodes were

* For bibliography see Berger, 1929, 1930; Fischer, 1932; Kornmüller, 1935; Gibbs, Davis and Lennox, 1935; Jasper and Andrews, 1936; Gerard, Marshall and Saul, 1936; and others.

** Kindly supplied by the Winthrop Chemical Company.

† Kindly supplied by Dr. R. C. de Bodo.

silver wires encased in a rubber tube. The cut sciatic nerve was inserted into this tube. These electrodes were connected with the secondary coil of a Harvard inductorium. In circuit with the primary (activated by a 1.5 volt dry cell) was a hand operated mercury contact key and a string galvanometer signal device. The stimuli were make and break shocks spaced from one to three seconds apart, and usually followed by a rapid series of six or eight shocks (by hand). The ipsilateral nerves to the hamstring muscles were left intact so that a flexor response of the lower leg might occur and be recorded on a smoked drum. The strength of the stimulating current was adjusted to give approximately a maximal response. Two levels of anesthesia were arbitrarily chosen and studied in detail: (a) The lightest anesthesia it was possible to work with without producing a disturbing generalized muscular response, on stimulating the sciatic nerve, and (b) The level at which the flexion reflex just disappeared. These two levels cover a wide anesthesia range; the former represents the surgical stage (stage III, plane 1) of anesthesia, while the latter represents deep surgical (stage III, plane 3) anesthesia. For brevity, hereafter, these two levels will be referred to as light and deep anesthesia.

Electrodes. The concentric electrodes described by Beecher, McDonough, and Forbes (1938) were used. These are made of silver supported on a hard rubber base. The grid lead is spike shaped and protrudes 2 mm. beyond the base. It is everywhere insulated except at its tip. At the base it is surrounded by the ground lead, a circular band 1 mm. in width and 6 mm. in outside diameter. The electrodes were freshly chlorided electrolytically each time before use. With these, potential differences were recorded between the surface of the cortex and 2 mm. deep in the interior. When these electrodes are used the ground lead fills a large part of the opening in the skull made necessary in order to identify the desired cortical position. Herniation of the brain is thus in large measure prevented and the arterial and respiratory pulsations minimized. The potential difference appears to be somewhat greater when led off in this manner (interior to surface) than when both leads, though the same distance apart, are applied to the surface. The increased potentials tend to give a clearer recording of changes.

Amplifier. The potential differences between the grid and ground leads were amplified by the direct coupled apparatus described by Forbes and Grass (1937) and were recorded on film with a Hindle string galvanometer. Ten milliseconds units were recorded by a timer on one margin of the film. The signal device recorded the stimuli on the opposite margin.

Results

Frequency and voltage. The standard deviation of the mean* frequency has been calculated in all cases, and is invariably given. It, however, does not show the constancy of the frequency counts from experiment to experiment. The striking constancy of this is shown only in detailed tables which, to conserve space, have not been presented here.

In the case of nitrous oxide, data are given only for light anesthesia, for at normal atmospheric pressures deep anesthesia under this agent is of course impossible without severe anoxia of the tissues accompanying the anesthesia. In all cases care was taken to avoid anoxia.

When frequencies per sec. of the cortical action waves are given, the counts have been made by two observers in all cases, and the two results averaged. They rarely differed by more than two or three waves per sec. Every deflection was counted as a wave. Care was taken to avoid 60-cycle

* This is derived by the standard statistical formulae:

$$\text{S. D. (individual)} = \sqrt{\frac{\Sigma D^2}{N-1}} = x; \quad \text{S. D. (mean)} = \frac{x}{\sqrt{N}}$$

To test for significant difference: $M_1 - M_2 > 2\sqrt{\overline{\text{S.D.}}^2_{m1} + \overline{\text{S.D.}}^2_{m2}}$

interference. In each observation activity was usually recorded continuously for 5 to 10 sec. A full second was counted in each case; the seconds, though arbitrarily chosen for counting, were spread out as well as possible over the entire experiment at the given level of anesthesia. Unless otherwise specified, the frequencies listed indicate the total count for all discernable waves irrespective of type. On the average, 38 counts were made in duplicate for

Table 1.† Mean frequency per second of cortical waves during anesthesia.*
(With Standard Deviations)

Agent	Light Anesthesia		Deep Anesthesia	
		Including Occasional Large Waves		Including Occasional Large Waves
Nitrous oxide	43.2 ±0.7			
Cyclopropane	42.9 ±0.6		42.0 ±0.7	
Ether	39.9 ±0.4		38.5 ±0.4	
Divinyl ether	37.1 ±0.5		34.9 ±0.6	
Ethylene	36.7 ±0.4		37.2 ±0.5	
Trichlorethylene	33.3 ±0.5		32.7 ±0.4	
Ethyl alcohol	31.3 ±0.5		30.9 ±0.3	
Ethyl chloride	30.5 ±0.5		28.8 ±0.4	
Ethyl urethane	30.4 ±0.4		29.4 ±0.3	
Chloroform	28.7 ±0.3		26.2 ±0.5	
Amylene hydrate	26.5 ±0.5		24.9 ±0.4	
Tribromethanol	22.2 ±0.6	27.0 ±0.6	22.3 ±0.5	22.9 ±1.0
"Evipal"	21.6 ±0.7	22.1 ±0.9	18.3 ±0.7	18.2 ±0.8
Paraldehyde	19.8 ±0.3	22.2 ±0.5	21.0 ±0.4	22.3 ±0.5
Sodium Barbital	18.7 ±0.4	20.5 ±0.9	17.7 ±0.4	18.3 ±0.9
Chloralosane	13.6 ±0.3	14.2 ±0.3	13.3 ±0.4	13.6 ±0.4
"Nembutal"	13.5 ±0.4	15.2 ±0.4	13.6 ±0.7	15.3 ±0.8

* Under several agents bursts of cortical activity occur. These bursts appear about every three to five seconds and are followed by relatively quiescent periods. The agents which show this phenomenon and the frequency per second of the large waves during such periods of activity, are as follows: Tribromethanol, 12; "evipal," 9; paraldehyde, 5; sodium barbital, 8; "nembutal," 8. (The frequency is the same during both light and deep anesthesia.)

† Derbyshire *et al.* (1936) reported a faster frequency for "nembutal" than we have found. In view of this discrepancy additional experiments were performed. These experiments (in addition to those listed above) furnished counts agreeing with those presented in Table 1. Apparently the figure given by Derbyshire represents a maximum frequency whereas ours is based upon the average count for an entire second.

each level of anesthesia for each agent, and 22 counts were made in duplicate for each experiment with each agent, 11 being under light anesthesia and 11 under deep. For those agents which give rise to bursts of large waves, in addition to the small ones, the means and their standard deviations have been calculated not only for the *total* wave count but also for the small waves alone, omitting the large waves of the bursts in this particular case. The frequency of the large waves *during* the bursts has also been determined for those agents which show the phenomenon. "Small" waves refers to the

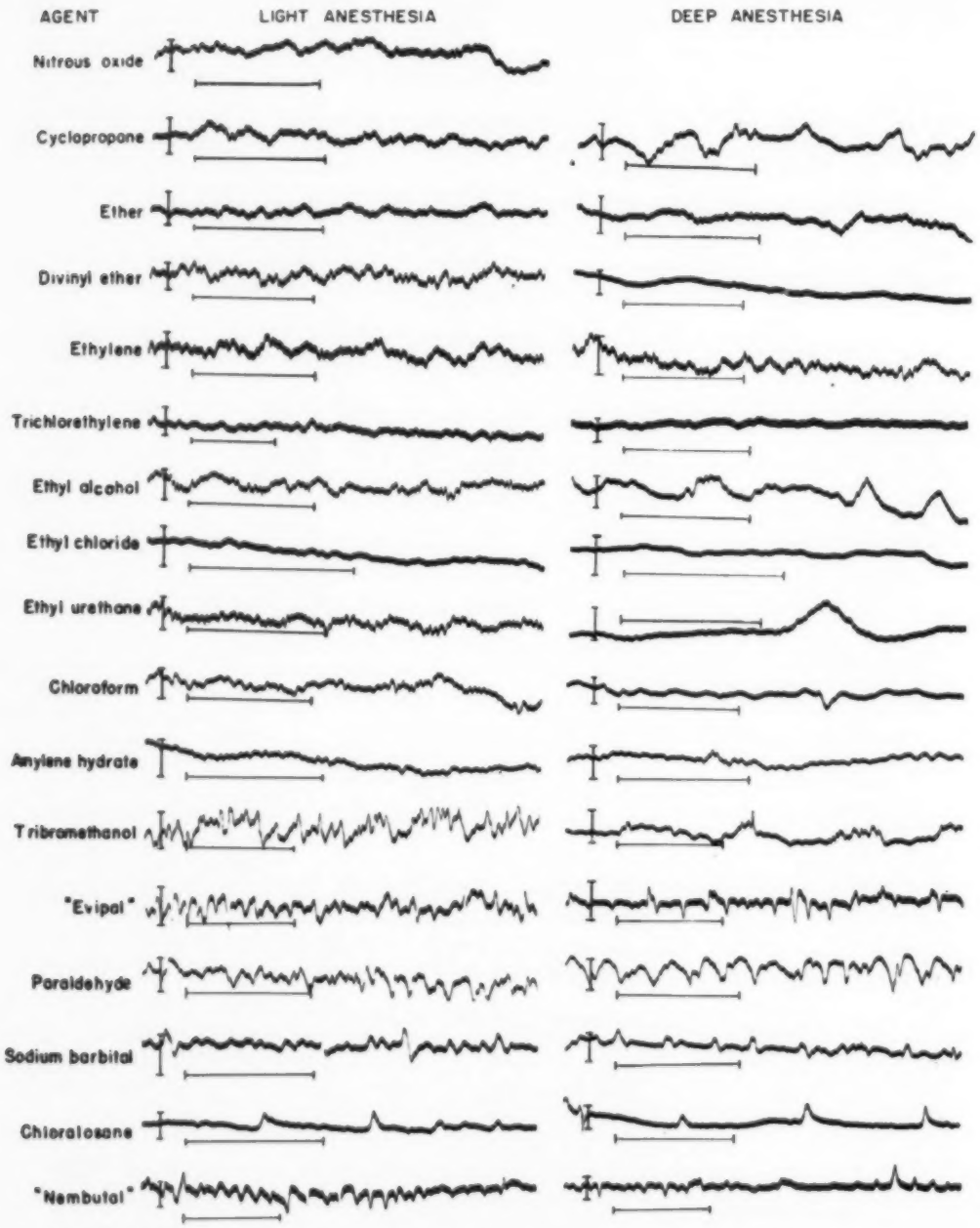


FIG. 1. Typical records of cortical action potentials obtained under each of the agents studied at both light and deep levels of anesthesia. An upward excursion signifies negative potential of the grid lead. This was always the central electrode which penetrated the cortex. Read from left to right. The vertical line (sensitivity) in each case represents 200 μV, and the horizontal line 1 sec.

typical, regular fine waves as distinguished from the less frequent bursts of very large waves. The voltages for these are given in the Table 2, which follows. The mean frequencies per second with their standard deviations are presented in Table 1 and Fig. 2.

The data have further been analyzed as to voltage and frequency of the waves for both light and deep anesthesia before and after sciatic stimulation. The entire mass of data has not been analyzed as to the effect of sciatic stimulation on the voltage of the cortical waves. One experiment for each

Table 2. Effects of sciatic stimulation on the voltage of cortical waves (microvolts) during anesthesia.*

Agent	Voltage—Light Anesth.		Voltage—Deep Anesth.		Volt. Occasional Large Waves Light Anesth.		Volt. Occasional Large Waves Deep Anesth.	
	Before Stim.	After Stim.	Before Stim.	After Stim.	Before Stim.	After Stim.	Before Stim.	After Stim.
Nitrous oxide	21	46						
Cyclopropane	30	49	22	23				
Ether	24	48	18	17				
Divinyl ether	10	15	9	9				
Ethylene	14	23	9	7				
Trichlorethylene	17	37	13	12				
Ethyl alcohol	18	43	15	15				
Ethyl chloride	15	24	4	5				
Ethyl urethane	28	41	22	20				
Chloroform	20	41	15	14				
Amylene hydrate	18	27	14	15				
Tribromethanol	34	34	15	14	147	152	114	105
"Evipal"	22	21	13	13	86	83	43	45
Paraldehyde	28	28	16	14	94	92	84	75
Sod. barbital	19	17	12	14	92	95	206	213
Chloralosane	15	15	10	10	87	85	97	106
"Nembutal"	17	17	12	9	69	71	51	47

* Average, see text.

agent has been considered. In measuring voltages the amplitude of 4 to 6 typical blocks (strips of film 1 to 3 cm. in length) have been measured where possible. These 4 to 6 values have been averaged and are presented in Table 2 and in Fig. 3. Figure 3 does not include the large waves. Stimulation had no effect on their voltage, in the cases studied.

The mean frequencies of the cortical waves before and after sciatic stimulation are presented in Table 3. This division of the data increases the error inherent in the mean values as a result of the smaller number of individuals involved and is reflected in the larger standard deviations. Even so, the relative smallness of the standard deviations and the uniformity of the results obtained indicate that such division of the data is permissible. Sciatic stimulation does not alter the frequency.

Table 4 contains data presented in Fig. 4, demonstrating the relationship

Table 3. Mean frequency per second of cortical waves before and after sciatic stimulation. (With Standard Deviations)

Agent	Waves	Anesth. Level	Frequency Before Stim.	Frequency After Stim.
Nitrous oxide	All	Light	43.5 ±0.9	42.9 ±1.0
Cyclopropane	All	Light	43.7 ±1.0	42.8 ±0.7
	All	Deep	42.1 ±1.1	42.1 ±1.1
Ether	All	Light	39.9 ±0.5	40.2 ±0.8
	All	Deep	38.0 ±0.5	39.7 ±0.6
Divinyl ether	All	Light	38.7 ±0.8	37.5 ±0.5
	All	Deep	35.8 ±1.3	35.0 ±0.9
Ethylene	All	Light	36.9 ±0.6	36.5 ±0.5
	All	Deep	37.6 ±0.8	37.5 ±0.4
Trichlorethylene	All	Light	32.8 ±0.8	32.9 ±0.7
	All	Deep	32.8 ±0.6	32.4 ±0.7
Ethyl alcohol	All	Light	32.1 ±0.9	31.0 ±0.8
	All	Deep	30.0 ±0.5	30.9 ±0.6
Ethyl chloride	All	Light	30.4 ±1.1	27.5 ±0.7
	All	Deep	29.9 ±0.6	28.4 ±0.9
Ethyl urethane	All	Light	29.9 ±0.5	29.8 ±0.9
	All	Deep	29.7 ±0.6	29.3 ±0.7
Chloroform	All	Light	28.8 ±0.4	29.0 ±0.6
	All	Deep	26.9 ±0.8	26.4 ±0.5
Amylene hydrate	All	Light	26.3 ±1.5	25.3 ±1.5
	All	Deep	24.9 ±0.7	25.3 ±0.6
Tribromethanol	Small	Light	22.7 ±0.7	21.0 ±1.6
	Small	Deep	21.7 ±0.4	24.1 ±0.8
	All	Light	27.3 ±0.8	27.0 ±1.3
	All	Deep	25.9 ±1.9	26.8 ±1.1
"Evipal"	Small	Light	20.2 ±1.0	24.3 ±0.9
	Small	Deep	18.7 ±1.4	18.5 ±3.2
	All	Light	23.2 ±1.0	24.3 ±0.9
	All	Deep	20.6 ±0.8	19.3 ±2.9
Paraldehyde	Small	Light	20.1 ±0.5	19.1 ±0.7
	Small	Deep	21.4 ±0.9	22.2 ±1.0
	All	Light	25.3 ±0.7	23.1 ±0.5
	All	Deep	22.8 ±1.2	22.2 ±1.0
Sodium barbital	Small	Light	19.4 ±1.5	19.0 ±0.7
	Small	Deep	17.8 ±0.6	16.2 ±1.6
	All	Light	23.6 ±1.1	22.2 ±1.5
	All	Deep	21.4 ±1.0	22.0 ±1.3
Chloralosane	Small	Light	13.7 ±0.4	13.1 ±0.6
	Small	Deep	13.5 ±0.5	12.8 ±0.7
	All	Light	15.0 ±0.4	13.8 ±0.6
	All	Deep	14.2 ±0.7	13.6 ±0.3
"Nembutal"	Small	Light	13.6 ±0.5	13.1 ±0.8
	Small	Deep	16.0 ±0.6	13.3 ±1.7
	All	Light	14.8 ±0.5	14.9 ±1.0
	All	Deep	17.8 ±1.4	16.4 ±2.2

of voltage of cortical waves to depth of anesthesia. As already described, the depth of anesthesia was arbitrarily chosen on the basis of the response of lower leg flexion to central sciatic stimulation. The excursion made by the recording lever on a smoked drum was measured in millimeters. The voltage of the cortical waves just preceding the stimulation was measured in microvolts as described above (in obtaining data for Table 2). Though data on only one experiment under each agent are presented, numerous others were measured: 3 experiments for ether, 7 for cyclopropane, 2 for ethylene and so on. When the voltages are to be compared over even a short period of time

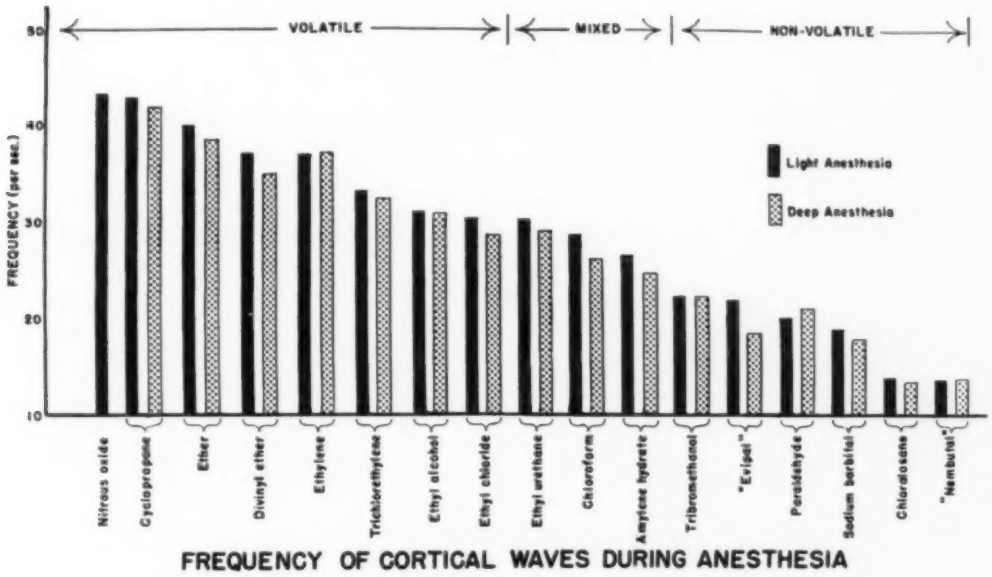
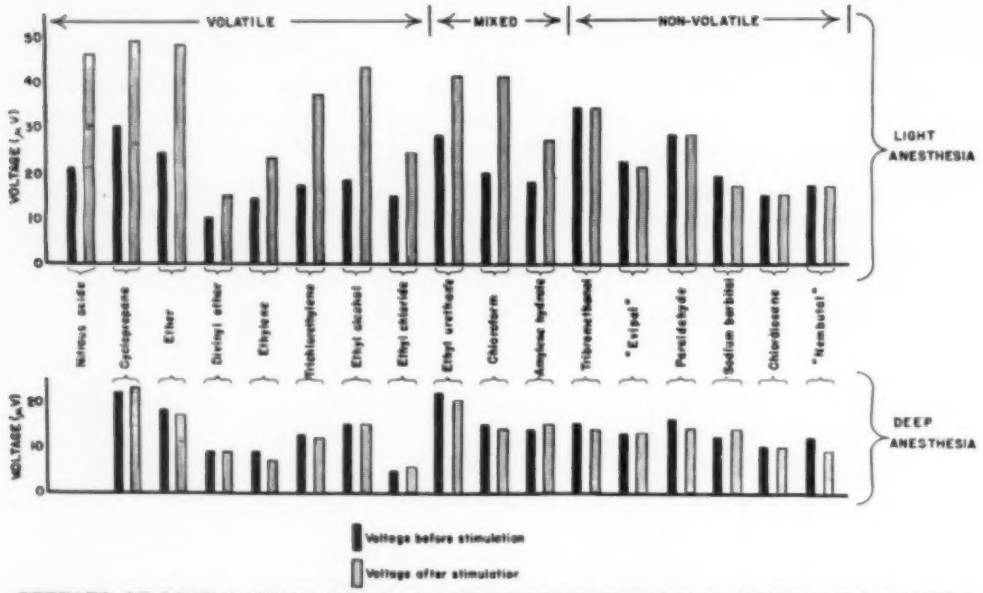


FIG. 2. This figure is based upon the fine waves. It seemed better to compare like waves. In any case, a similar figure prepared from the total wave count data would be little different from this. See Table 1.

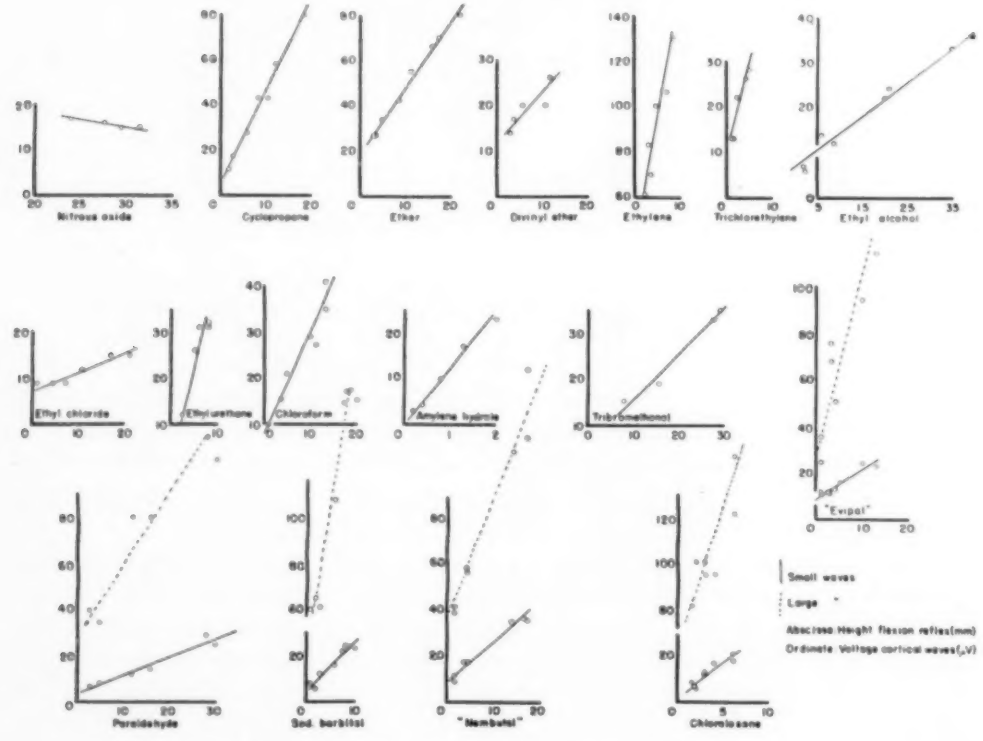
it is necessary that the following several factors be kept constant: Amplification of the voltages, the galvanometer string tension (corrected on the basis of frequent calibrations), the strength and duration of the stimulus producing the reflex, the reflex recording apparatus, and the general condition of the animal, with particular attention to adequate oxygenation.

Pattern. While it is impossible to choose a strip of film only a few centimeters long which will demonstrate all characteristics of the action potentials for a given agent, in Fig. 1 sample records are presented and, though they are considerably reduced in size, it is evident they can be divided into two distinct classes: First, there is the group composed of nitrous oxide, cyclopropane, ether, divinyl ether, ethylene, trichlorethylene, ethyl alcohol, ethyl chloride, ethyl urethane, chloroform, and amylene hydrate. These, with the exception of ethyl urethane are volatile agents, and the frequency



EFFECTS OF SCIATIC STIMULATION ON THE VOLTAGE OF CORTICAL WAVES DURING ANESTH.

FIG. 3. Data do not include large waves. See Table 2.



Relation of Voltage of Cortical Waves to Depth of Anesthesia

FIG. 4. See Table 4.

Table 4. Relation of the voltage of cortical waves to the depth of anesthesia.

(As measured by the height of a flexion reflex)

Date	Agent	Film No.	Time	Voltage of Cortical Waves* (μV)	Height of Flexion Reflex (mm.)
3/25/38	Nitrous oxide	100	2:51	15	29.5
		101	2:53	15	31.5
		102	3:03	17	24.0
		109	3:09	16	27.7
3/25/38	Cyclopropane	58	12:34	12	2.0
		59	12:35	18	3.0
		60	12:36	28	6.0
		61	12:37	43	8.5
		62	12:38	43	11.0
		63	12:39	58	12.3
		65	12:41	80	18.5
		66	12:42	100	21.5
3/25/38	Ether	13	11:38	27	3.0
		14	11:39	27	3.5
		15	11:40	34	5.0
		17	11:43	42	8.7
		19	11:46	55	11.2
		22	11:49	66	15.9
		24	11:53	70	17.2
		26	11:57	80	22.0
3/25/38	Divinyl ether	110	3:22	14	3.0
		111	3:23	17	3.8
		112	3:23½	20	5.8
		113	3:24	20	10.7
		114	3:25	26	11.8
3/28/38	Ethylene	12	12:19	61	2.2
		14	12:22	70	3.9
		16	12:24	83	3.2
		18	12:27	100	4.7
		19	12:30	106	7.0
		20	12:31	130	8.5
12/29/37	Trichlorethylene	23	3:39	13	1.5
		25	3:44	13	1.8
		26	3:46	22	2.5
		27	3:55	26	4.5
		28	3:59	28	5.3
4/28/38	Ethyl alcohol	8	12:01	33	35.0
		10	12:05	36	40.0
		27	12:31	24	21.0
		29	12:33	22	20.0
		32	12:42	12	8.5
		36	12:49	14	6.0
		42	1:04	6	2.5
		45	1:09	7	2.0

Table 4 (Cont.). Relation of the voltage of cortical waves to the depth of anesthesia.
(As measured by the height of a flexion reflex)

Date	Agent	Film No.	Time	Voltage of Cortical Waves* (μV)	Height of Flexion Reflex (mm.)
7/18/38	Ethyl chloride	13	10:44	15	17.0
		14	10:45	15	21.0
		16	10:50	12	10.8
		18	10:51	9	7.2
		23	11:00	9	4.7
		25	11:02	9	1.0
5/ 2/38	Ethyl urethane	4	10:54	26	5.0
		14	11:14	31	6.0
		15	11:24	31	8.0
		16	11:34	32	8.0
		22	11:54	12	2.5
		28	12:07	10	2.5
1/ 5/38	Chloroform	5	12:23	10	1.0
		7	12:32	15	4.0
		8	12:35	21	5.0
		10	12:38	29	10.0
		11	12:40	27	11.0
		12	12:42	35	13.0
		13	12:44	41	13.0
5/ 9/38	Amylene hydrate	9	11:13	23	2.0
		11	11:18	17	1.3
		14	11:20	10	0.8
		17	11:23	4	0.4
		19	11:25	3	0.2
				Small Waves / Large Waves	
5/13/38	Tribromethanol	2	1:12	15 / 200	8.0
		3	1:13	19 / 240	15.5
		4	1:14	35 / 260	29.0
		5	1:16	33 / 220	27.5

per sec. under light anesthesia is in every case above 26. The group is characterized by rapid, fine waves. Then there is the other group composed of tribromethanol, "evipal," paraldehyde, sodium barbital, chloralosane, and "nembutal." Here the agents are all "non-volatile,"† having slow total frequencies. The pattern is characterized by large slow waves (1 to 10 per sec.) on which small waves are superimposed. Though the figure does not show it well, these large waves tend to come in bursts* every 3 to 5 sec., and each burst lasts 1 or 2 sec. Between the bursts the galvanometer is comparatively quiet. The characteristic patterns for the two groups remain consistent and distinct throughout all levels of anesthesia, as long as activity can be re-

† That is, can not be administered by inhalation.
* Except in the case of chloralosane.

Table 4 (Cont.). Relation of the voltage of cortical waves to the depth of anesthesia.
(As measured by the height of a flexion reflex)

Date	Agent	Film No.	Time	Voltage of Cortical Waves* (μV)			Height of Flexion Reflex (mm.)
				Small	Large	Bursts	
4/ 7/38	"Evipal"	2	11:00	23	116	102	13.0
		5	11:15	24	95	125	10.0
		11	11:47	16	—	128	5.0
		12	12:02	13	50		4.0
		18	12:40	11	76		3.0
		20	12:46	11	68		3.0
		22	12:56	12	36		1.0
		24	1:03	11	25		1.0
7/28/38 A.M.	Paraldehyde	12	11:55	29	115	129	28.0
		14	11:56	25	105	136	30.0
		19	12:24	17	80	126	16.0
		20	12:34	12	80		12.0
		21	12:47	8	35		5.0
		22	12:51	7	40		3.0
4/11/38	Sodium barbital	11	2:50	23	150	280	10.0
		13	2:55	24	154	356	8.0
		14	2:58	24	155	328	8.8
		16	3:05	22	149	363	7.3
		19	3:14	16	108	340	5.5
		21	3:26	12	61	261	2.5
		24	3:43	6	65	279	1.5
		26	3:46	8	60	360	0.5
7/ 8/38	Chloralosane	6	2:32	21	122		6.0
		8	2:43	18	147		6.0
		14	3:09	13	96		3.0
		15	3:14	17	96		4.0
		16	3:19	12	101		3.0
		21	3:36	6	101		2.0
		22	3:39	7	—		1.8
		24	3:44	9	82		1.5
2/ 7/38	"Nembutal"	9	11:54	35	109	145	14.0
		12	12:01	36	115	—	17.0
		24	12:13	36	144	168	17.0
		48	2:14	17	58	105	4.0
		56	2:45	17	56	103	4.0
		66	3:16	11	41	83	1.5
		67	3:19	9	39	79	1.5

* Average for all waves unless otherwise specified.

corded. The consistency to type of anesthetic agent persists regardless of how often a given animal may be shifted from one agent to another. *Consistency of pattern is a fundamental characteristic of the behavior of the electrical activity in the cortex under a given anesthetic agent.* Detailed frequencies and voltages for each agent are given in Tables 1 and 2.

Secondary cortical discharges (see Forbes and Morison, 1939) in response to central sciatic stimulation have been found under amylene hydrate, tribromethanol, "evipal," paraldehyde, sodium barbital, chloralosane, and "nembutal." The first two compounds listed are the components of "avertin"; Derbyshire, Rempel, Forbes and Lambert (1936) reported the presence of the phenomenon under this agent, as they also did under "nembutal." The secondary cortical discharges were not found under the other agents.

Discussion

Frequency. A number of points emerge from the foregoing mass of data. The chief ones will be considered forthwith: Each anesthetic agent (see Table 1) conditions a fundamental frequency of cortical waves; determined under given conditions (animal, position and type of electrodes) this is a constant within fairly narrow limits. The frequency remains essentially unaffected throughout a wide range of anesthesia depth. In one or two cases there is a slight tendency to slowing with increase in depth of anesthesia. This may conceivably be due to the dropping out of waves of muscular origin although the arrangement of the electrodes is such as to render this improbable. In any case the change is so slight as to be of questionable significance.

It is not possible to say on the basis of the present data that there is a frequency which is only characteristic of a given anesthetic agent. For example, the difference between the mean frequency per second for nitrous oxide, 43.2 ± 0.7 is certainly not significantly different from that for cyclopropane, 42.9 ± 0.6; yet there is unquestionably a significant difference between that for nitrous oxide and ether. In this case the difference of the means is *four* times the square root of the sum of the squares of the standard deviations. In other words, it is twice as much as it would need to be for bare significance. Frequently the difference between adjacent agents in Table 1 is not significant; whereas in agents once removed the frequency usually is significantly different.

Table 3 shows that neither under light nor under deep anesthesia can sciatic stimulation affect the frequency under any of the agents studied. We can be certain that this lack of effect was not due to failure of the stimulus to reach the cortex, for in Table 2 and Fig. 3 it is apparent that the stimuli employed did reach the cortex and altered the voltages of the waves in the "volatile" and "mixed" groups while the secondary discharges associated with all of the agents in the "non-volatile" groups indicate that here also pathways to the cortex were open.

With anesthesia deeper than that employed in this study, the voltage of the waves is so reduced it becomes difficult and finally impossible to distinguish the waves; so for deep levels of anesthesia, as far as we can detect with present apparatus, the frequency does finally slow down: the waves disappear before death. *But the fact remains that for a given agent, within the range of anesthesia depth employed clinically the frequency is remarkably con-*

stant, being relatively characteristic for a given agent and little changed by alterations of depth over a wide range and unaffected by peripheral stimuli (sciatic).

When the frequencies are tabulated in order, as they are in Table 1 and Fig. 2, a further interesting point becomes evident; *viz.*, the agents with the highest cortical frequencies are highly volatile. As the frequency decreases, in general so also does the volatility, so that the non-volatile anesthetic agents appear at the opposite end of the list.

It is interesting to observe in the case of the non-volatile agents that the frequency of the cortical beat approaches more nearly to that found in unanesthetized animals. Derbyshire *et al.* (1936) found in unanesthetized, dozing cats that the cortical potentials showed a dominant pattern of about 6 waves per sec. with a voltage of about 60 μV. Superimposed upon these waves there were smaller excursions at about 14 per sec. total of 20. We have found under light "evipal" anesthesia a total frequency of 22 with a voltage of the large waves of 86.

In addition to these similarities in frequency, similarities in pattern have been observed. Derbyshire *et al.* (1936) have called attention to the great amplitude of the large slow waves under "nembutal." The appearance of these under the barbiturate, as they point out, resembles like waves which develop with the onset of natural sleep. Bremer (1937) has also insisted that barbiturate narcosis closely resembles natural sleep. Clinicians have long been aware of the similarity of barbiturate hypnosis and narcosis and natural sleep. Indeed, almost invariably patients on going under "evipal" anesthesia yawn, and every surgeon knows that if he starts his surgical procedure before this yawn occurs he is likely to disturb his patient to such an extent it will be difficult to get him satisfactorily "asleep" without using an unusually great quantity of the anesthetic. A comparison of cortical frequencies offers some objective evidence that narcosis by means of the non-volatile anesthetic agents is more nearly akin to natural sleep than that induced by the volatile agents.

Voltage. We have seen that the frequency of the cortical waves is a relatively stable characteristic of the animal under a given anesthetic agent. The voltage, however, is rather labile. Table 2 and Fig. 3 show that under light anesthesia central sciatic stimulation greatly increases (50 to 140 per cent) the voltage of the cortical waves under nitrous oxide, cyclopropane, ether, divinyl ether, ethylene, trichlorethylene, ethyl alcohol, ethyl chloride, ethyl urethane, chloroform, and amylene hydrate. This confirms the observation of Derbyshire *et al.* (1936) for ether. From Fig. 3 it is apparent that this response to stimulation is characteristic of agents in the "volatile" and "mixed" groups. It is lost abruptly as soon as the "non-volatile" group is entered.

The table and figure also demonstrate that in no case with any agent does stimulation alter the voltages under deep anesthesia. The table also shows that voltage of the large waves which is found in the non-volatile group is

unaffected by the sciatic stimulation; yet this lack of effect on voltage is not due to failure of impulses to reach the cortex, for it is in this very group that the secondary discharges are outstandingly apparent.

Table 4 and Fig. 4 demonstrate the close relationship between voltage of cortical waves and depth of anesthesia as measured by the height of a flexion reflex following sciatic stimulation. Except in the case of the occasional large waves there is a striking linear relation shown on graphing the data. This relationship is extraordinarily close considering the possibilities of error in measurement. Even with the occasional large waves the linear nature of the curve is clearly apparent. Waves appearing in bursts do not seem to be as uniformly depressed.

The large quantity and variety of data presented *show a clear correlation between the response of the sensory cortex and the discharge of the spinal motor neurones. The cortical voltages are not simply unrelated phenomena arising from isolated centers.*

The voltage of cortical waves under anesthesia, then, is a labile characteristic easily affected in the case of some agents by peripheral stimuli, but not affected in others, a characteristic uniformily altered by changes in depth of anesthesia.

General. There is a striking tendency for the anesthetic agents to fall into the same two groups when tested by various criteria. Any far-reaching speculation on such a basis is unwarranted, of course; but it is interesting to call attention to the common qualities of the agents of each group. A consideration of the common characteristics of the members of each group is not intended to imply that there are not many differences between the individual members. Rioch and Rosenblueth (1935) for example, have pointed out differences in the action of several non-volatile anesthetic agents.

Secondary cortical discharges (for a discussion of this phenomenon, see Forbes and Morison, 1939) in response to sciatic stimulation are *not* found under nitrous oxide, cyclopropane, ether, divinyl ether,* ethylene, trichlorethylene, ethyl alcohol, ethyl chloride, ethyl urethane, or chloroform anesthesia.

Secondary discharges *do* appear in response to sciatic stimulation under amylene hydrate, tribromethanol, "evipal," paraldehyde, sodium barbital, chloralosane, and "nembutal" anesthesia.

It is interesting to observe that no secondary discharges were elicited under any agent having a fundamental frequency of cortical waves (total) above 28 per sec., while the secondary discharge could be elicited regularly in all of the agents having a frequency below 28. In the former group, the agents are predominantly volatile, whereas, in the latter they are mainly non-volatile.

Though the separation of the agents into similar distinct groups on the basis of alteration of a flexion reflex is not so clear cut, it is interesting to

* On one or two occasions waves suggestive of a secondary discharge appeared in response to stimulation under divinyl ether anesthesia. These were never definite.

recall in passing (as previously reported by Beecher, McDonough and Forbes, 1939) that a sustained, *cumulative* reflex contraction of the leg flexors is regularly found upon repeated central stimulation of the sciatic nerve under one group of anesthetic agents: Nitrous oxide, cyclopropane, ether, ethylene, trichlorethylene, ethyl alcohol, ethyl chloride, ethyl urethane, chloroform and amylene hydrate. In the earlier paper it was pointed out that the reflex under these agents is of the same type as it is in the decerebrate animal. On the other hand it was found (*loc. cit.*) under another group of agents: "evipal," sodium barbital, "nembutal" and chloralosane, that the flexion reflex response was like that which appears following sciatic stimulation in an animal after low transection of the spinal cord. The reflex here was characterized by large, isolated, *non-cumulative* twitches in response to central sciatic stimulation. The remainder of the agents did not fall as clearly into the two groups; with divinyl ether, tribromethanol and paraldehyde sometimes one type of flexion response occurred and sometimes another. The type of response elicited seems to depend upon depth of anesthesia.

The outstanding difference between the two distinct types of flexion reflex appears to be a matter of after-discharge. This is in harmony with the conclusions of Bremer and Moldaver from studies of a frog's spinal reflex (1934). With the first group, the ether-like group, the after-discharge following stimulation is little if at all reduced and the flexion response rises in a cumulative fashion as a result of the prolonged stimulation. With the second group, the barbiturate-like group, the after-discharge is greatly reduced, and the increased response to each stimulus appears as an isolated twitch of the muscle.

If the widely accepted view is correct that after-discharge is due to internuncial neurones which, through "long-circuiting" of sensory impulses provide for a prolonged stimulation of the ventral horn cells after the original excitation has ceased, then the latter group is distinguished by curtailment of the long-circuiting of sensory impulses.

When the agents are divided on the basis of the presence or absence of a secondary discharge following stimulation, the resulting two groups are rather strikingly similar to the two groups which can be made by dividing the anesthetics on the basis of type of reflex response to stimulation. There are two discrepancies here but one cannot help wondering if they may not be more apparent than real, due to experimental inadequacy rather than to fundamental difference. For example, divinyl ether at certain levels of anesthesia gives the non-cumulative type of flexion response and it has been pointed out earlier that under this agent waves suggestive of the secondary discharge appeared in response to sciatic stimulation. These were not clear-cut, and we have placed this agent in the group not showing such phenomena, since we failed to elicit an unmistakable secondary discharge. Perhaps this is an error. The other discrepancy concerns amylene hydrate. Here, clear-cut secondary discharges were produced, but not the non-cumulative

type of flexion reflex. But as already pointed out (Fig. 2) amylene hydrate is a border-line agent, falling adjacent to tribromethanol when the agents are grouped on a basis of descending frequency of cortical waves.

With these two apparent or real discrepancies present, it cannot be said that invariably with the agents under which the secondary discharges can be elicited one also gets a non-cumulative type of flexion response to stimulation, but it can be said that this is almost always the case.

When the agents are divided on the basis of whether or not sciatic stimulation affects the voltage of cortical waves, again groups are obtained which

Table 5. The agents are arranged on the basis of descending frequency of cortical waves. "1" signifies characteristic of Group I and "2" of Group II.

Agent	Molecular Size	Volatility	Frequency	Voltage	Pattern	Response to Sciatic Stimulation	Secondary Discharge	Flexion Reflex
Nitrous oxide	1	1	1	1	1	1	1	1
Cyclopropane	1	1	1	1	1	1	1	1
Ether	1	1	1	1	1	1	1	1
Divinyl ether	1	1	1	1	1	1	1 (?)	1 and 2*
Ethylene	1	1	1	1	1	1	1	1
Trichlorethylene	1	1	1	1	1	1	1	1
Ethyl alcohol	1	1	1	1	1	1	1	1
Ethyl chloride	1	1	1	1	1	1	1	1
Ethyl urethane	1	2	1	1	1	1	1	1
Chloroform	1	1	1	1	1	1	1	1
Amylene hydrate	1	1	1	1	1	1	2	1
Tribromethanol	2	2	2	2	2	2	2	1 and 2*
"Evipal"	2	2	2	2	2	2	2	2
Paraldehyde	2	2	2	2	2	2	2	1 and 2*
Sod. barbital	2	2	2	2	2	2	2	2
Chloralosane	2	2	2	2	2	2	2	2
"Nembutal"	2	2	2	2	2	2	2	2

* The type of flexion response varies, apparently with depth of anethesia.

are strikingly similar to the preceding ones. The same thing is also generally true when the agents are divided on the basis of volatility, relatively light or heavy molecules, voltage, frequency and similar pattern. The two similar groups which appear when the agents studied are tested by 8 diverse criteria in Table 5.

As far as the criteria considered here are concerned, and notwithstanding certain discrepancies,† the rather strikingly uniform character of the two groups leads, then, to the question of whether the eight similar characteristics of each group are in any case more than chance. Typical characteristics of the *first group:* High volatility; low molecular weight; low voltage of all waves; high frequency of cortical waves; similar pattern; no secondary cortical discharge following sciatic stimulation; cumulative flexion reflex,

† Table 5 is useful in emphasizing the discrepancies.

perhaps meaning normal long-circuiting of sensory impulses; under light anesthesia sciatic stimulation alters the voltage of cortical waves, but not under deep. For the *second group:* Low volatility; high molecular weight; high voltage of many waves; low frequency of cortical waves; similar pattern; a secondary cortical discharge following sciatic stimulation; non-cumulative flexion reflex, perhaps meaning greatly reduced long-circuiting of sensory impulses; even under light anesthesia sciatic stimulation does not affect the voltage of cortical waves here.

Any attempt to identify a common factor in the 8 characteristics of each group must be speculative. It is interesting to consider what significance, if any, there may be in the correlation between the greater reverberation and after discharge in Group I than in Group II, the increased voltage following sciatic stimulation in light anesthesia in Group I (absent in Group II), and the higher frequency of cortical waves in Group I than in Group II. The reverberation hypothesis easily accounts for the difference in type of spinal reflex observed, if one holds the widely accepted view that after-discharge is the result of continued stimulation of the ventral horn cells brought about by the long-circuiting of impulses through internuncial neurones after the original excitation has ceased, for the outstanding difference between the two types of reflex response seems to be a matter of after-discharge. The basic difference between the action of the two groups *may* be a matter of the possibilities for long-circuiting or reverberation of impulses in the central nervous system. Such a hypothesis is mainly speculative with only a little experimental evidence to support it.

Gerard and his coworkers suggested (1936) that anesthesia may "suspend awareness by lessening cellular activity or disrupting the whole active pattern." Perhaps the foregoing material points the way, at least to some extent, to how this occurs. The principal findings which have been enumerated and discussed are strikingly consistent; but interpretation of them is difficult, if not impossible as yet. These findings, we believe, must be reckoned with in any final interpretation of the electrical activity of the cortex.

Summary

1. Seventeen anesthetic agents, nitrous oxide, cyclopropane, ether, divinyl ether, ethylene, trichlorethylene, ethyl alcohol, ethyl chloride, ethyl urethane, chloroform, amylene hydrate, tribromethanol, "evipal," paraldehyde, sodium barbital, chloralosane, and "nembutal" have been studied in the cat. Following exposure of the right posterior sigmoid gyrus of the cortex, recording electrodes of the concentric type were placed on the sensory area, in all cases. Factors compared were pattern, frequency, and voltage of the cortical action potentials, as well as the response of these factors to sciatic stimulation at the several levels of anesthesia. Simultaneous spinal activity was recorded by means of the flexion reflex. Two levels of anesthesia were considered in particular: (a) light, the lightest anesthesia it was possible to work with without producing a disturbing generalized muscular re-

sponse on stimulating the sciatic nerve; (b) deep, the level at which the flexion reflex just disappeared.

2. The frequency per second for each agent at both light and deep levels of anesthesia has been determined and the mean with its standard deviation listed in all cases (Table 1, Fig. 2). For a given agent within the range of anesthesia depth employed clinically, the frequency is remarkably constant, being relatively characteristic for a given agent and little changed by alterations of depth over a wide range of anesthesia (Table 1) and unaffected by peripheral stimuli (sciatic), Table 3. When the frequencies are tabulated in order of size it is apparent that, in general, high frequencies are associated with highly volatile agents and low frequencies with non-volatile agents. Attention is called to the fact that the pattern and frequencies associated with the non-volatile agents are similar to those found during natural sleep. The generalization can be made that frequency of the total cortical waves is a relatively stable characteristic during anesthesia.

3. During *light* anesthesia under "Group I" agents (nitrous oxide, cyclopropane, ether, divinyl ether, ethylene, trichlorethylene, ethyl alcohol, ethyl chloride, ethyl urethane, chloroform and amylene hydrate), sciatic stimulation greatly increases the voltage of the cortical waves (Table 2, Fig. 3). It is also apparent there that even under light anesthesia, at least of the level used in this study, central sciatic stimulation has no effect on the voltage of the cortical waves under the "Group II" agents (tribromethanol, "evipal," paraldehyde, sodium barbital, chloralosane, and "nembutal"). Group I consists of volatile agents (excepting the urethane), and Group II of non-volatile.

Stimulation has no effect on the voltage of the typical cortical waves under any agent at a deep level of anesthesia. Attention is called to the fact that failure of stimulation to alter the voltages of any of the waves under the non-volatile agents is not due to failure of impulses to reach the cortex for "secondary discharges" occur here in response to stimulation even (and usually) at deep levels of anesthesia. This indicates that pathways remain open. There is a close linear relationship between voltage of cortical waves and depth of anesthesia as measured by the magnitude of the flexion reflex following central sciatic stimulation (Table 4, Fig. 4). The cortical voltages are a fundamental general characteristic of the cortex and not simply phenomena arising from isolated centers. The voltage of cortical waves under anesthesia is a labile characteristic easily affected in certain given cases by peripheral stimuli, but not affected in others, a characteristic uniformly altered by changes in depth of anesthesia.

4. Records showing typical action potentials for each agent at both light and deep levels of anesthesia are shown, Fig. 1. Here again, it is apparent on the basis of pattern, that the anesthetics studied fall into the two groups. The cortical waves are fine under Group I agents, fairly uniform in size, and of a frequency per second greater than 26 in all cases. In *Group II* small fine waves are superimposed on large slow waves. The large waves

tend to come in bursts (except chloralosane). Consistency of pattern is a fundamental characteristic of the behavior of the electrical activity in the cortex during anesthesia.

5. The seventeen agents studied show a tendency to fall into two groups when tested by several criteria, Table 5. The composition of the groups is strikingly similar whenever any of the characteristics is considered; *viz.*, molecular size, volatility, frequency per second of the cortical waves (fast or slow), voltage, pattern, presence or absence of secondary discharge following sciatic stimulation, type of flexor response to sciatic stimulation, ability of sciatic stimulation to alter the voltage of cortical waves under light anesthesia.

6. Possible implications and relationships of the above findings to each other are discussed.

This study was suggested by Dr. Alexander Forbes and we wish to express our thanks to him for his painstaking review of our data and his invaluable criticism of the manuscript.

REFERENCES

1. Beecher, H. K., McDonough, F. K., and Forbes. A. Effects of blood pressure changes on cortical potentials during anesthesia. *J. Neurophysiol.*, 1938, *1:* 324–331.
2. Beecher, H. K., McDonough, F. K., and Forbes, A. Similarity of effects of barbiturate anesthesia and spinal transection. *J. Neurophysiol.*, 1939, *2:* 81–88.
3. Berger, H. Über das Elektrenkephalogramm des Menschen. *Arch. Psychiat. Nervenkr.*, 1929, *87:* 527–570.
4. Berger, H. Ueber das Elektrenkephalogramm des Menschen. *J. Psychol. Neurol., Lpz.*, 1930, *40:* 160–179.
5. Bremer, F. Différence d'action de la narcose éthérique et du sommeil barbiturique sur les réactions sensorielles acoustiques du cortex cérébral. Signification de cette différence en ce qui concerne le mécanisme du sommeil. *C. R. Soc. Biol., Paris*, 1937, *124:* 848–852.
6. Bremer, F., and Moldaver, F. Étude de l' "Afterdischarge" réflexe des muscles toniques des anoures. *C. R. Soc. Biol., Paris*, 1934, *117:* 821–825.
7. Derbyshire, A. J., Rempel, B., Forbes, A., and Lambert, E. F. The effects of anesthetics on action potentials in the cerebral cortex of the cat. *Amer. J. Physiol.*, 1936, *116:* 577–596.
8. Fischer, M. H. Elektrobiologische Erscheinungen an der Hirnrinde. *Pflüg. Arch. ges. Physiol.*, 1932, *230:* 161–178.
9. Forbes, A., and Grass, A. M. A simple direct-coupled amplifier for action potentials. *J. Physiol.*, 1937, *91:* 31–35.
10. Forbes, A., and Morison, B. R. Cortical response to sensory stimulation under deep barbiturate narcosis. *J. Neurophysiol.*, 1939, *2:* 112–128.
11. Gerard, R. W., Marshall, W. H., and Saul, L. J. Electrical activity of the cat's brain. *Arch. Neurol. Psychiat., Chicago*, 1936, *36:* 675–735.
12. Gibbs, F. A., Davis, H., and Lennox, W. G. Electroencephalogram in epilepsy and in conditions of impaired consciousness. *Arch. Neurol. Psychiat., Chicago*, 1935, *34:* 1133–1148.
13. Jasper, H. H., and Andrews, H. L. Human brain rhythms: recording techniques and preliminary results. *J. gen. Psychol.*, 1936, *14:* 98–126.
14. Kornmüller, A. E. Die Bioelektrischen Erscheinungen architektionischer Felder der Grosshirnrinde. *Biol. Rev.*, 1935, *10:* 383–426.
15. Rioch, D. McK., and Rosenblueth, A. Inhibition from the cerebral cortex. *Amer. J. Physiol.*, 1935, *113:* 663–676.

THE CEREBRAL ACOUSTIC AREA OF THE CAT

A COMBINED OSCILLOGRAPHIC AND CYTOARCHITECTONIC STUDY

F. BREMER AND R. S. DOW*
Laboratoire de Pathologie Générale de l'Université Libre de Bruxelles

(Received for publication March 17, 1939)

INTRODUCTION

THE EXACT limits of the cortical acoustic area in mammals are not yet known. Previous workers, using anatomical, physiological or pathological methods have been unable to establish the boundaries with certainty and many conclusions have been contradictory, as the following historical note indicates.

HISTORICAL NOTE

One of the earliest anatomical observations pointing to the location of the cat's acoustic area was that of Vogt (1898), who discovered a separate area of early myelinization in the region of the middle ectosylvian gyrus. Cytoarchitectonic studies of the temporal cortex of the cat have been made by Campbell (1905), Winkler and Potter (1914) and Kornmüller (1933–1937), but there is no agreement among these investigators. Campbell divided the temporal cortex of the cat into two parts, the ectosylvian A and the ectosylvian B (Fig. 1a). He regarded the former as the primary acoustic area which received the projection from the medial geniculate body. Winkler and Potter attempted to apply Brodmann's (1909) classification of the temporal lobe to their study of the cat, but their division is difficult to follow and no map was prepared. Kornmüller has described in this region a sensory type of cortex (Fig. 1b) principally characterized by a well developed fourth layer and the arrangement of the cellular constituents of this granular layer in conspicuous radially oriented rows. As will be seen below, he correlated this cytoarchitectonic appearance with the area giving electrical potentials in response to sound. The cytoarchitectonic areas of the temporal region in other laboratory mammals have been studied by Droogleever Fortuyn (1914) in 9 rodents, Tsuneda (1937) in the mouse, and in monkeys by Walker (1937) and von Bonin (1938). All have found a localized area of sensory type of cortex which they have thought to be the acoustic projection area. This is probably homologous with the areas 41 and 42 of Brodmann's parcellation, which are located on the transverse temporal gyrus of Heschl in man.

Experimental anatomical methods have been applied to this problem by various workers, likewise without total agreement (Yoshido, 1924; Ohnishi, 1931, Posthumus Meyjes, 1934; and D'Hollander and Stoffles, 1937 on rabbits; Waller, 1934, and Pennington, 1937, rats; Poljak, 1932, Le Gros Clark 1936, and Walker 1937, and Rundles and Papez, 1938, monkeys). The majority is agreed that there is a point-to-point relationship between specific parts of the medial geniculate body and specific regions of the auditory projection area. According to Walker (1937), this area as determined by retrograde degeneration of the cells in the medial geniculate body after cortical ablation, corresponded to the area of "koniocortex" which he described on the surface of the temporal lobe lying within the sylvian fissure. The agreement, between the cytoarchitectonic sensory area and the projection area from the medial geniculate body as determined by the investigators mentioned above, is apparently not as close in rodents as in monkeys.

Poliak (1927) and Mettler (1932) studied the degeneration resulting from lesions in the temporal cortex of the cat. Mettler gave particular attention to the association fibers from this region, and concluded that, instead of spreading out in a centrifugal spray arrangement, there was a tendency for the fibers to be distributed in accordance with the

* Fellow of the Belgian-American Foundation 1937–38.

cytoarchitectonic areas as outlined by Campbell. Lesions indicated that ectosylvian area A (Fig. 1a) sends short association fibers in greatest number first to the rest of this area and next to the middle part of the ectosylvian gyrus. Large lesions of ectosylvian area A caused association fibers to the anterior and posterior parts of the ectosylvian gyrus and to the middle suprasylvian gyrus to degenerate in considerable numbers. An animal sacrificed 30 days after ablation of the ectosylvian area A had a retrograde degeneration to the homolateral medial geniculate body. It is not clear from this work whether all the auditory

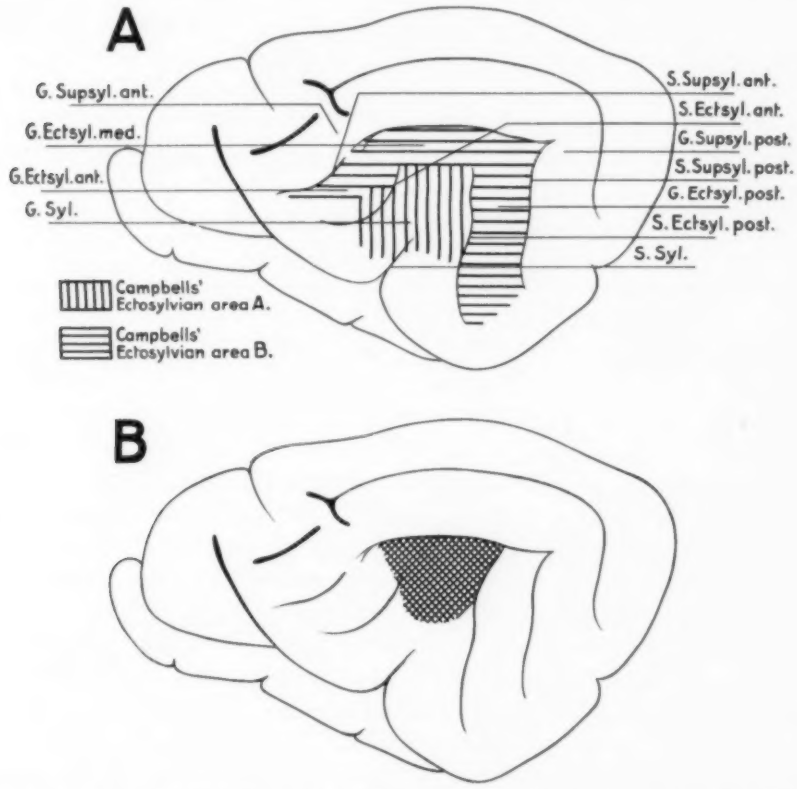


FIG. 1. A. Diagram of the lateral surface of the cat's cerebrum showing the sulci and gyri of the acoustic and surrounding areas. The cytoarchitectonic areas according to Campbell are given.

B. Cortical acoustic area in the cat according to Kornmüller. G. Ectsyl. ant., Anterior ectosylvian gyrus; G. Ectsyl. med. Middle ectosylvian gyrus; G. Ectsyl. post., Posterior ectosylvian gyrus; G. Supsyl. ant., Anterior suprasylvian gyrus; G. Supsyl. post., Posterior suprasylvian gyrus; G. Syl., Sylvian gyrus; S. Ectsyl. ant., Anterior ectosylvian sulcus; S. Ectsyl. post., Posterior ectosylvian sulcus; S. Supsyl. ant., Anterior suprasylvian sulcus; S. Supsyl. post., Posterior suprasylvian sulcus; S. Syl., Sylvian sulcus.

projection from the medial geniculate body terminates in the ectosylvian area A, or whether some may also go to the ectosylvian area B.

Ades, Culler and Mettler (1938) in a preliminary report of the degeneration resulting from lesions of the medial geniculate body in the cat, describe as the largest, and apparently only cortical, connection a group of efferent fibers to the sylvian cortex. A more complete report of the physiological findings in this interesting work has just appeared (Ades, Mettler and Culler, 1939) and the completion of the anatomical studies is eagerly awaited.

Woollard and Harpman (1939) working independently have described the cortical projection in 2 cats with electrolytic lesions in the medial geniculate body made with a

Horsley-Clarke apparatus. Using the Marchi method, fibers have been traced to the middle ectosylvian gyrus and the posterior part of the anterior ectosylvian gyrus together with the upper part of the anterior and posterior sylvian gyri. The inferior border lies a short distance above the rhinal fissure.

Cortical ablation experiments with subsequent observation of auditory ability have been made by Munk (1890) and Larionow (1899) and others in the dog, and by Wiley (1932) and Pennington (1937), using modern conditioned reflex technique, in the rat. The latter authors review the literature concerning this type of experiment. Clinical and pathological studies in man have been made by Henschen (1918), Pfeifer (1921) and Börnstein (1932), and myelogenetical studies by Flechsig (1920). The auditory center has been described by all these as sharply localized in the region of the transverse temporal gyrus, although there is disagreement concerning the presence or absence of tonal localization within the cortex.

Physiological methods have been applied to this problem since the work of Ferrier (1876) who was the first to report an area in the temporal region of the cat and other mammals, the stimulation of which caused a movement of the contralateral ear. He concluded that this was the region of the auditory sensory area. In recent years the oscillographic technique has been applied to this problem. Gerard, Marshall and Saul (1933) briefly described electrical potentials derived from the temporal cortex in monkeys in response to sound, and in 1936 the same authors found auditory responses in the cat in the cortical grey matter, in some instances the surface of the median and posterior ectosylvian and suprasylvian gyri, and in two instances the posterior splenial gyrus. Davis (1934) determined the acoustic area in the cat by the oscillographic recording of the response to brief interrupted sounds. The boundaries which he gave in the cat extend somewhat more posteriorly than the area given by Kornmüller (Fig. 1b). Kornmüller (1933) obtained electrical potential responses to sound from a localized area in the ectosylvian region in the cat and concluded that the limits of this area as mapped out physiologically corresponded to the cytoarchitectonic area which he described. In 1937 he published a diagram of the extent of this area together with a detailed description of the different layers of the cortex in this region.

The goal of the present work is to verify and render more exact this coincidence between the cytoarchitectonic area and the area responding to sound. This verification has been made particularly desirable by the recent communication of Ades, Culler and Mettler (1938, 1939) on the functional organization of the medial geniculate bodies in the cat. It is possible that some of the discrepancies in the results may be explained by the existence of a primary sensory area and a gnostic sensory cortex, between which a distinction cannot be made by the oscillographic method as at present applied.

METHODS

In the course of other work on the acoustic area in the cat, one of us (F. B.) has shown repeatedly, corroborating the work of Kornmüller (1933–1937), that the cortical potenials

in response to sound were best obtained from the area between and dorsal to the anterior and posterior ectosylvian sulci and ventral to the suprasylvian sulcus. When the animal is not anesthetized (method of "l'encéphale isolé") and with its brain in good functional condition, the cortical response to a brief sound stimulus is made up of two successive but distinct elements: (i) a large diphasic wave (Fig. 2 D. G.) and (ii) a more or less prolonged rhythmic after-discharge (Fig. 2 D, Bremer 1937 a and b, 1938). Of these two elements the primary wave is much more resistant, and as a consequence the more constant. Furthermore, the after-discharge has a tendency to irradiate to a distance from the source, as indicated by the primary wave. (Fig. 2 C.) This tendency to intracortical irradiation is still more marked when the stimulus is a prolonged sound, for example, a continuous pure tone. This is probably attributable to the phenomenon of summation or synaptic facilitation (Adrian, 1936). For these two reasons the observation and recording of the primary wave in response to a brief sound stimulus (click) is the best method to determine the cortical acoustic area. However, the assumption that the large primary wave provoked by a brief sound stimulus characterizes oscillographically the area of projection of the geniculate-cortical fibers is only an assumption. Certain arguments of probability may be invoked in its behalf. The demonstration, in confirmation of that of Kornmüller, of the coincidence of the cortical region thus deliminated with a well defined cytoarchitectonic area of sensory structure would lend support to this assumption.

In the two experiments here reported the exact boundaries of the area giving response to "clicks" was determined by systematically moving the cotton electrodes until the borders of the responsive area were located. This was done either by moving both the bipolar electrodes so that the line joining them was parallel to the expected boundaries of the region, or by placing one electrode well off the acoustic area (indifferent electrode) and moving the second in every direction, until the boundaries were located. The former method gave the sharpest boundaries. Throughout the experiments care was taken to maintain the distance between the electrodes as constant as possible, in order to eliminate all variation of amplitude of registered potentials which could be caused by a difference in the electrical resistance of the tissue between the two electrodes. The points tested were carefully marked on a sketch of the exposed area and the presence or absence of response was recorded for each spot, as well as repeated visual observations without recording on the camera. The electrocorticogram was registered with a Dubois oscillograph and a five-stage amplifier coupled with condensors of 0.1μF. The necessary sections of brains were fixed in 95 per cent alcohol, embedded in celloidin, sectioned serially at 25μ thickness and stained with the Nissl or with a dark Van Gieson techniques. In one brain every 25th section was mounted and in the other 2 sections were mounted in every 25, one being stained with the Nissl technique and the other with a dark Van Gieson for myelin sheaths. The cytoarchitectonic areas were mapped out in each case.

Experimental Results

The results in Experiment 1 are presented in tabular form in the following protocol. The points explored are marked by letter on the diagram Fig. 3a and the letters correspond to the records shown in Fig. 2.

Experiment 1. Cat, Jan. 1, 1938. Sensitivity 10 mm. per 100 μV. Both bipolar and "monopolar" derivation as described above were used. The indifferent electrode was placed on the posterior suprasylvian gyrus. Records made using "monopolar" derivation.

Point	Location	Trials recorded	Response
A	Anterior suprasylvian gyrus	1	None
B	Middle suprasylvian gyrus	2	Slight to none
C	Anterior ectosylvian gyrus	1	Slight
D	Middle ectosylvian gyrus	4	Marked
E	Posterior ectosylvian gyrus (superior part)	3	Moderate to absent
F	Posterior ectosylvian gyrus (middle part)	1	None
G	Sylvian gyrus	1	Marked

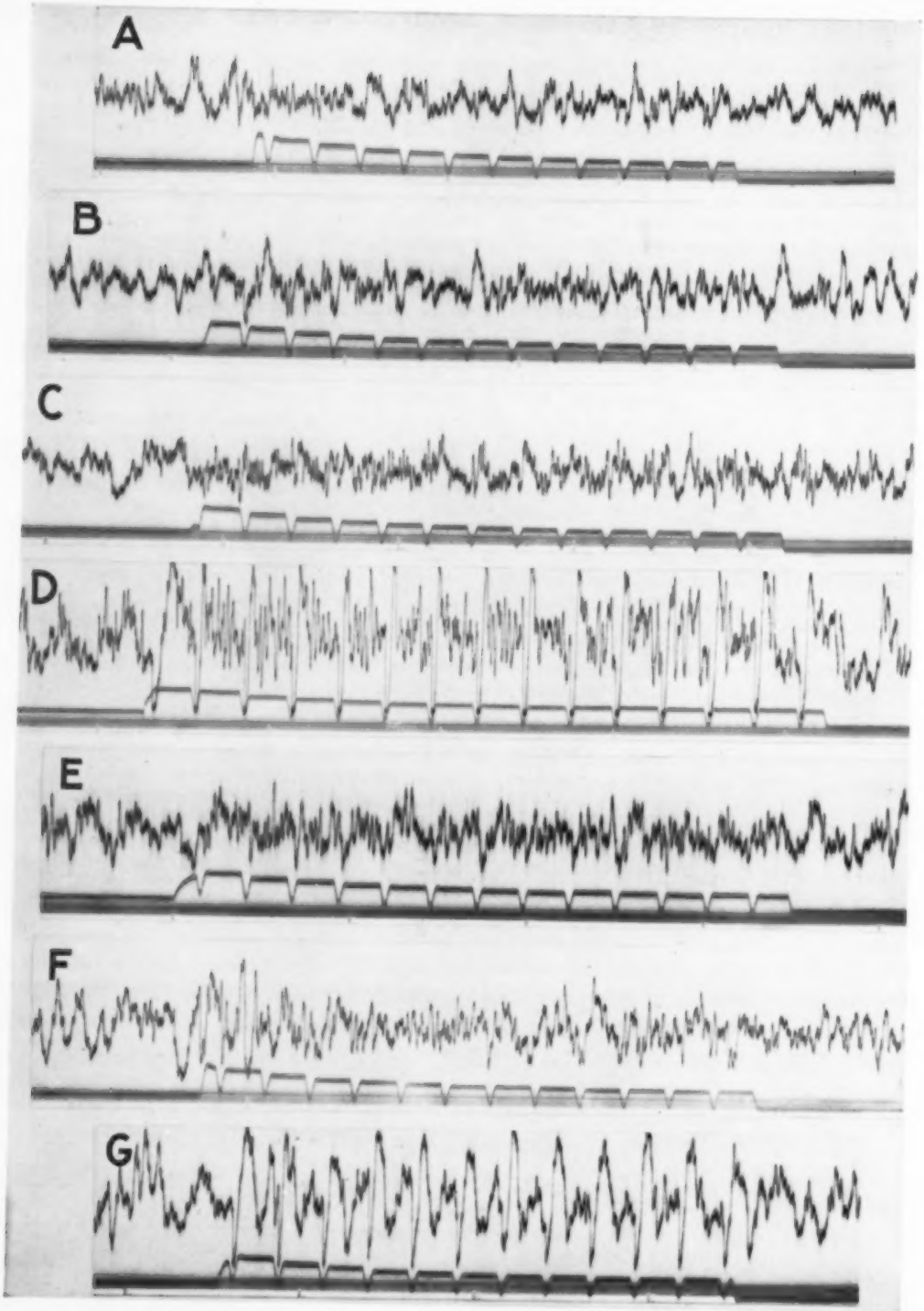


FIG. 2. The responses of the acoustic cortex to "clicks" in Exp. 1. "Monopolar" leading. Sensitivity 10 mm. per 100 μV. Original reduced $\frac{1}{2}$. The letters refer to the diagram Fig. 3a and indicate the position of the lead electrode when the record was taken. Records from above downward show: (i) electrocorticogram, (ii) signal of the occurrence of the "clicks" and (iii) time in seconds. For other explanations see text.

Figure 2, a reproduction of some of the records demonstrates the marked differences in response resulting from slight changes in the position of the active lead. Record C shows the response of the cortex at the anterior bor-

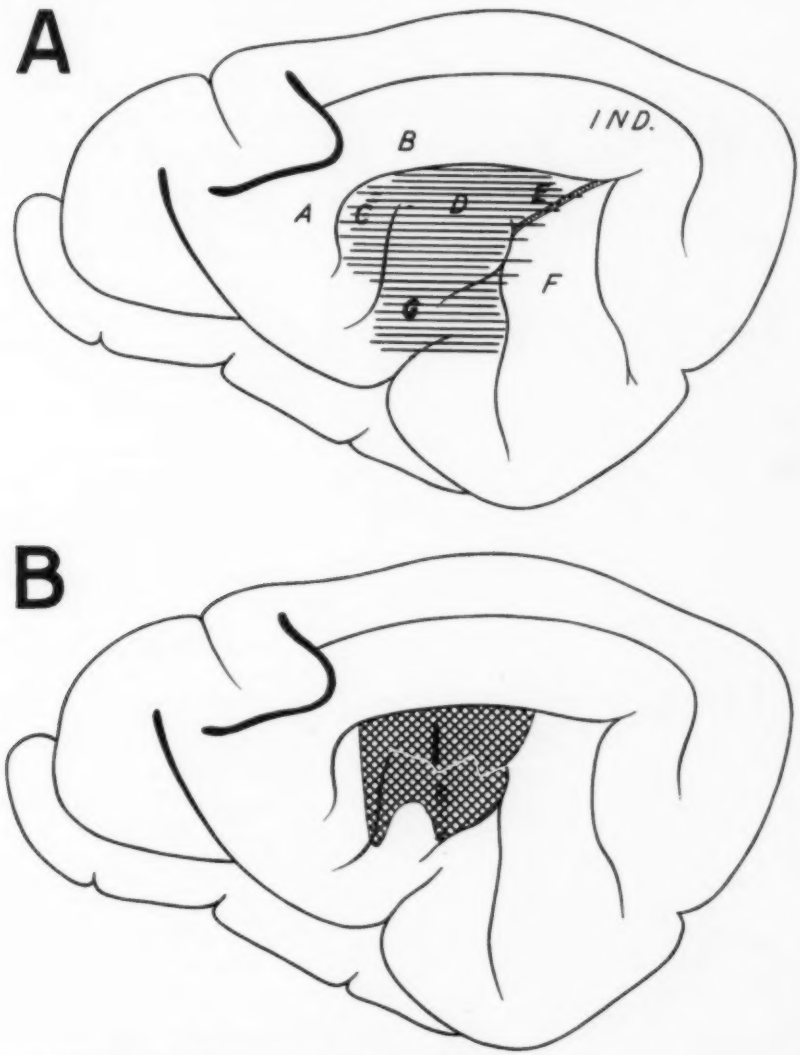


FIG. 3. Diagrams of the cortical markings in Exp. 1.

A. The area giving responses indicated by shaded area. Letters A to G indicate the points from which the records were taken which are shown in Fig. 2.

B. The cytoarchitectonic area as mapped out in Exp. 1. The vertical line within the area indicates the site of the microphotograph shown in Fig. 4.

der of the area (point C, Fig. 3A) with a definite acceleration of the spontaneous waves, without primary waves in response to the "clicks." This phenomenon, which is probably the expression of the intracortical irradiation of the after-discharge, is entirely absent in record A taken from a lead

on the anterior suprasylvian gyrus (point A, Fig. 3A). This point is only a few millimeters in front of point C. In the record E from the posterior border of the responsive area (point E, Fig. 3A) the primary waves are visible, but are small when compared with the same waves in records D and G taken from the center and inferior part of the area. Records B and F, taken respectively from the middle supra-sylvian gyrus and middle part of the posterior ecto-sylvian gyrus (points B and F, Fig. 3A), show an absence of response, save for a slight acceleration of the spontaneous waves of the corticogram.

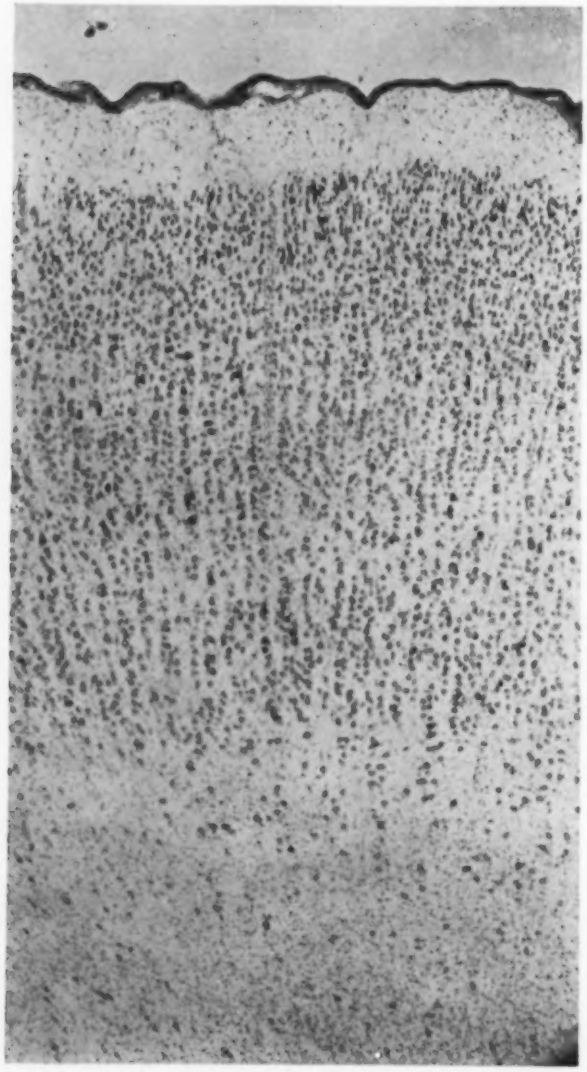


FIG. 4. Microphotograph of a portion of section taken from Exp. 1. The section is from the middle ecto-sylvian gyrus within the acoustic area. 50 ×.

The shaded area in Fig. 3A is the total extent of the responsive area. The cortical area having cytoarchitectonic characteristics of a "sensory" cortex makes up "b" in Fig. 3. This cortex has a broad internal granular layer, the cells of which are arranged in conspicuous radial rows and a markedly reduced internal pyramidal layer. A section from the middle ectosylvian gyrus in the center of the acoustic area is shown in Fig. 4. It is generally agreed among students of cytoarchitectonics that the boundaries of the various areas in the cat are less clearly defined than in many other mammals, including certain rodents. This is particularly true of the temporal cortex which even in primates is more difficult to divide than are other lobes with sensory areas.* (von Bonin, 1938)

* The authors are indebted to Dr. A. E. Kornmüller who kindly confirmed our identification of this area and who checked the boundaries of the area in a few of our own sections.

The results in Experiment 2 are given in the following tabular protocol. The points explored are indicated by number on both the table and the diagram, Fig. 5A. In this case both electrodes were placed on the active region being about 4 mm. apart. The position of the figures in the diagram (Fig. 5A) indicates a central point between the two electrodes. Points 1 to 7 are with the line between the two electrodes vertical, and thus parallel to the anterior and posterior borders of the active area. Points 8 to 13 are with the line between the two electrodes horizontal, and thus parallel with the superior and inferior borders of the acoustic area.

Experiment No. 2. Cat, Mar. 15, 1938. Sensitivity 10 mm. per 100 μV. Records made with bipolar derivation. Points refer to numbers on diagram, Fig. 5A.

Point	Location	Trials Recorded	Response
1	Posterior border of the posterior ectosylvian gyrus	2	None
2	Posterior ectosylvian gyrus	3	None
3	Boundary between middle ectosylvian and posterior ectosylvian	3	Marked
4	Middle ectosylvian gyrus	1	Marked
5	Middle ectosylvian gyrus	1	Marked
6	Anterior ectosylvian gyrus	1	Moderate, but irregular and without after-discharge
7	Anterior boundary of the anterior ectosylvian gyrus	1	None
8	Middle suprasylvian gyrus	2	None
9	Middle ectosylvian gyrus	5	Marked
10	Middle ectosylvian gyrus	2	Marked
11	Boundary between middle ectosylvian gyrus and sylvian gyrus	1	Marked
12	Superior border of sylvian gyrus	3	Marked
13	Sylvian gyrus	3	Moderate

The extent of the acoustic area as determined by histological methods is presented in Fig. 5B. The close correspondence between the cytoarchitectonic area and that giving potential responses is obvious in all except the inferior boundary. This may be explained by the difficulties in leading from the depths of the cortical exposure without touching more dorsal regions. In other more favorable experiments the inferior boundary has also been found to correspond to the inferior border of the sensory area, as outlined histologically in these two cases. The authors are in agreement with Kornmüller (1937) in regard to the histological and physiological boundaries of the acoustic area in the cat. We are unable to confirm the cytoarchitectonic areas as given for the cat by Campbell (1905) or Winkler and Potter (1914). The study of association fibers in this region by Mettler (1932) seemed to conform to the parcellation as given by Campbell. However, in view of the fact that the largest number of short association fibers leaving the sylvian gyrus went to the middle ectosylvian gyrus, this might be interpreted as

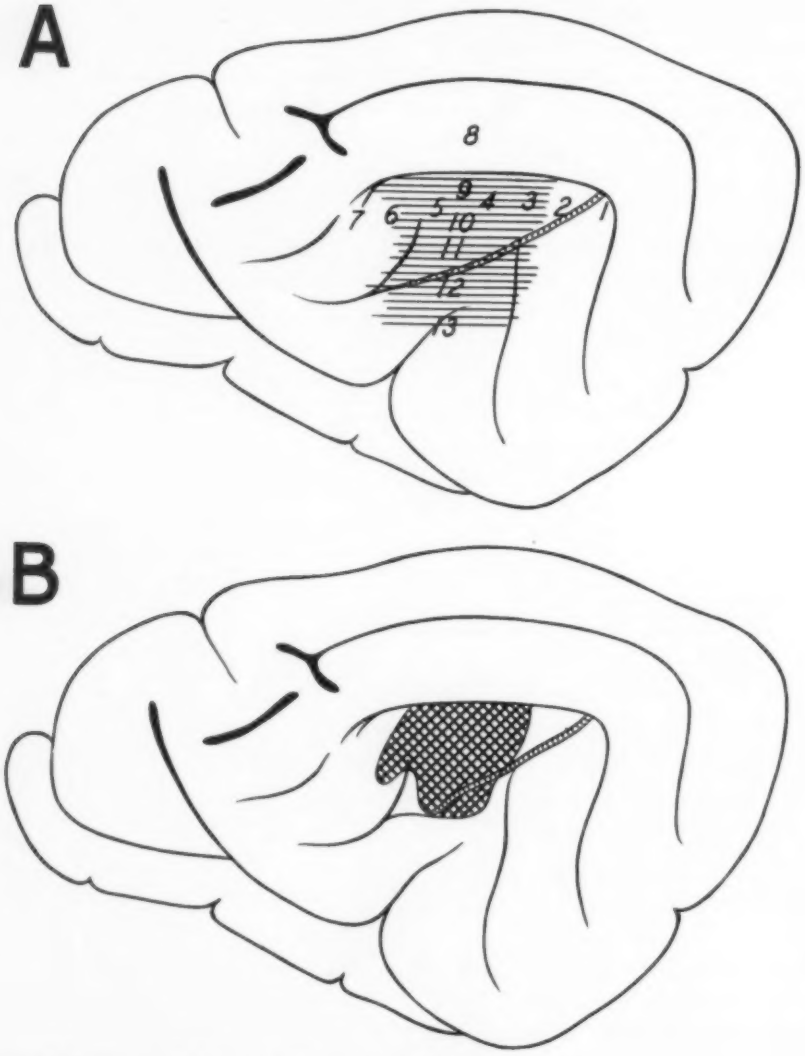


FIG. 5. Diagrams of the cortical markings in Exp. 2.

A. The area giving responses indicated by the shaded area. The numbers 1 to 13 indicate the points tested with "bipolar" electrodes and refer to the numbers in the tabular protocol of Exp. 2.

B. The cytoarchitectonic acoustic area as mapped out in Exp. 2.

supporting the present delimination. Of utmost importance will be the findings of Ades and his collaborators with the use of the Horsley-Clarke apparatus concerning the exact limits of the projection from the medial geniculate bodies after isolated lesions there. The cerebral acoustic area here described is identical with the area of projection of the fibers from the medial geniculate body as recently determined in two cats by Woollard and Harpman (1939).

In confirming the boundaries of this area we do not wish to infer that it

is necessarily strictly uniform in cytoarchitectonic structure. Indeed, more rigid criteria than we have been able to apply to this limited material will possibly show the existence of subdivisions within the acoustic area thus deliminated.

Conclusions

1. The boundaries of the area giving responses to auditory stimuli as determined by Kornmüller in the cat have been confirmed. These boundaries correspond to definite cytoarchitectonic boundaries. The whole area giving responses, although similar in structure, may not prove to be a uniform field when more rigid criteria for division are applied.

2. This area includes the upper part of the sylvian gyrus, the posterior part of the anterior ectosylvian gyrus and the middle ectosylvian gyrus. It is thought that this region represents the auditory projection area in the cat.

REFERENCES

Ades, H. W., Culler, E. A., and Mettler, F. A. Functional organization of the medial geniculated bodies of the cat. *Anat. Rec.*, 1938, *70:* 3 (Proc.)

Ades, H. W., Mettler, F. A., and Culler, E. A. Effect of lesions in the medial geniculate bodies upon hearing in the cat. *Amer. J. Physiol.*, 1939, *125:* 15–23.

Adrian, E. D. The spread of activity in the cerebral cortex. *J. Physiol.*, 1936, *88:* 127–161.

Börnstein, W. Teilfunktionen oder Einheitsfunktion im kortikalen Hörzentrum? *Mschr. Psychiat. Neurol.* 1932, *81,* 353–379.

von Bonin, G. The cerebral cortex of the cebus monkey. *J. comp. Neurol.*, 1938, *69:* 181–227.

Bremer, F. Etude oscillographique des activités sensorielles du cortex cérébral. *C. R. Soc. Biol., Paris,* 1937a, *124:* 842–847.

Bremer, F. L'activité cérébrale au cours du sommeil et de la narcose. Contribution à l'étude du mécanisme du sommeil. *Bull. Acad. Méd. Belg.*, 1937b, 68–86.

Bremer, F. Analyse oscillographique des réponses sensorielles de l'aire acoustique corticale chez le chat. *C. R. Soc. Biol., Paris,* 1939, *130:* 257–261.

Brodmann, K. *Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues.* Leipzig, J. A. Barth, 1909; reprinted, 1925, 324 pp.

Campbell, A. W. *Histological studies on the localisation of cerebral function.* Cambridge, University Press, 1905, 360 pp.

Clark, W. E. Le Gros. The thalamic connections of the temporal lobe of the brain in the monkey. *J. Anat., Lond.*, 1936, *70:* 447–464.

Davis, H. The physiological phenomena of audition. *Handbook of General Experimental Psychology.* Worcester, Mass., Clark Univ. Press, 1934, 962–998.

D'Hollander, F., et Stoffels, J. Nouveau procédé de localisation pour les recherches sur le cortex cérébral: Le palliogramme. *J. belge Neurol. Psychiat.*, 1937, *37:* 1–24.

Droogleever Fortuyn, A. B. Cortical cell-lamination of the hemispheres of some rodents. *Arch. Neurol. Psychiat., Lond.*, 1914, *6:* 221–354.

Ferrier, D. *The functions of the brain.* London, Smith-Elder & Co., 1876, xv, 323 pp.

Flechsig, P. *Anatomie des menschlichen Gehirns und Rüchenmarks auf myelogenetischer Grundlage.* Leipzig, Thieme, 1920, 121 pp.

Gerard, R. W., Marshall, W. H., and Saul, L. J. Cerebral action potentials. *Proc. Soc. exp. Biol., N. Y.*, 1933, *30:* 1123–1125.

Gerard, R. W., Marshall, W. H., and Saul, L. J. Electrical activity of the cat's brain. *Arch. Neurol. Psychiat., Chicago* 1936, *36:* 675–738.

Henschen, S. E. Über die Hörsphäre. *J. Psychol. Neurol., Lpz.*, 1918, *22:* 319–474.

Kornmüller, A. E. Bioelektrische Erscheinungen architectonischer Felder. Eine Methode der Lokalisation auf der Grosshirnrinde. *Dtsch. Z. Nervenheilk.*, 1933, *130:* 44–60.

KORNMÜLLER, A. E. *Die bioelektrischen Erscheinungen der Hirnrindenfelder mit allgemeineren Ergebnissen für Physiologie und Pathophysiologie des zentralnervösen Griseum*, Leipzig, Thieme, 1937, 118 pp.

LARIONOW, W. Ueber die musikalischen Centren des Gehirns. *Pflüg. Arch. ges. Physiol.*, 1899, *76:* 608–625.

METTLER, F. A. Connections of the auditory cortex of the cat. *J. comp. Neurol.*, 1932, *55:* 139–183.

MUNK, H. *Über die Functionen der Grosshirnrinde.* Berlin, Hirschwald, 1890, 320 pp.

OHNISHI, G. Über die zentrale Hörsbahn; besonders die Beziehung zwischen dem Temporallappen und dem Corpus geniculatum mediale. *Okayama-Igakkai-Zasshi*, 1931, *43:* 1959–1980. Ref. in *Neurol. Zbl.*, 1932, *62:* 248.

PENNINGTON, L. A. The function of the brain in auditory localization. II. The effect of cortical operation upon original learning. *J. comp. Neurol.*, 1937, *66:* 415–442.

PFEIFER, R. A. Die Lokalisation der Tonskala innerhalb der kortikalen Hörsphäre des Menschen. *Mschr. Psychiat. Neurol.*, 1921, *50:* 7–48, 99–108.

POLJAK, S. An experimental study of the association, callosal and projection fibers of the cerebral cortex of the cat. *J. comp. Neurol.*, 1927, *44:* 197–258.

POLJAK, S. *The main afferent fiber systems of the cerebral cortex of primates.* Berkeley, Calif., Univ. Calif. Press., 1932, xiv, 370 pp.

POSTHUMUS MEYJES, F. E. Recherches expérimentales sur l'anatomie du système acoustique central. *Encéphale*, 1934, *29:* 433–465.

RUNDLES, R. W., and PAPEZ, J. W. Fiber and cellular degeneration following temporal lobectomy in the monkey. *J. comp. Neurol.*, 1938, *68:* 267–296.

TSUNEDA, N. Zur Cytoarchitektonik des Neocortex des Mäusegehirns. *Folia anat. japon.*, 1937, *15:* 1–47.

VOGT, O. Sur la myélinisation de l'hémisphére cérébral du chat. *C. R. Soc. Biol., Paris*, 1898, *10:* 54–56.

WALLER, W. H. Topographical relations of cortical lesions to thalamic nuclei in the albino rat. *J. comp. Neurol.*, 1934, *60:* 237–269.

WOOLLARD, H. H., and HARPMAN, A. The cortical projection of the medial geniculate body. *J. Neurol. Psychiat., Lond.* 1939, *2 n.s.*, 35–44.

WALKER, A. E. The projection of the medial geniculate body to the cerebral cortex in the macaque monkey. *J. Anat., Lond.*, 1937, *71:* 319–331.

WILEY, L. E. The function of the brain in audition. *J. comp. Neurol.*, 1932, *54:* 109–141.

WINKLER, C., and POTTER, A. *An anatomical guide to experimental researches on the cat's brain.* Amsterdam, Versluys, 1914, 35 pl.

YOSHIDA, I. Über den Ursprung der kortikopetalen Hörbahn beim Kaninchen. *Folia anat. japon.*, 1924, *2:* 289–296.

FACTORS FOR FACILITATION AND EXTINCTION IN THE CENTRAL NERVOUS SYSTEM*

J. G. DUSSER de BARENNE AND W. S. McCULLOCH
Laboratory of Neurophysiology, Yale University School of Medicine, New Haven, Conn.

(Received for publication March 17, 1939)

CONTENTS

PAGE

INTRODUCTION 319
METHODS 320
RESULTS 321
A. *Necessity of antecedent neural excitation* 321
B. *Multiplicity of factors* 322
C. *Factors for facilitation and extinction* 325
1. Changes in electrical activity 326
a. in immediate neighbourhood of cortical stimulation 326
b. in neighbouring foci 326
c. in more remote parts of cortex 328
d. in distant parts of CNS 329
2. Slow voltage drifts 331
3. Changes in pH of cortex 334
D. *Mode of action of factors for facilitation and extinction* 336
1. Relation of latency and threshold 337
2. Dissociation of latency and amplitude 338
3. Influence of parameters of stimulation 339
a. Duration 339
b. Pattern-frequency 340
c. Pulse-frequency 341
d. Voltage 342
4. Triple stimulation 343
E. *Predictions* 343
1. Conditions for reversal of a cortical focus 343
2. Changes in knee-jerk 347
DISCUSSION 349
CONCLUSIONS 353
REFERENCES 354

INTRODUCTION

THE PHENOMENON now known as "facilitation" was discovered in 1881 by Bubnoff and Heidenhain[7] who observed that, with an interval of only a few seconds, repetition of supraliminal stimulation of a "motor" focus of the cerebral cortex elicited a larger peripheral response with shorter latency, and even that repetition of subliminal stimulation could bring in a response. They also demonstrated augmentation of motor response to cortical stimulation by antecedent cutaneous stimulation of the limb in which the response occurred. These phenomena are called facilitation. Facilitation of

* Aided by a grant from the Fluid Research Fund of Yale University School of Medicine. The expenses of the experiments on pH have been defrayed by a grant from the Child Neurology Research (Friedsam Foundation).

motor response can also be induced by antecedent stimulation of a neighbouring allied cortical focus (Graham Brown's "secondary facilitation"). What is common in all these instances is that *antecedent stimulation* has so altered the functional condition of the central nervous system (CNS) that the response to subsequent stimulation (*i.e.* to *test stimulation*) is changed in the direction of *more* response. To produce this effect the antecedent stimulation must excite, and we define here as factors for facilitation any changes of the CNS caused by antecedent excitation and causing a fall in threshold, a decrease in latency, an increase in amplitude or any combination of these.

The phenomenon designated "extinction," discovered in 1934 by the present authors, is a diminution or absence of response on repetition of stimulation of a "motor" focus within an interval longer than that required for facilitation. The latency of a partially extinguished response is markedly greater than of that to test stimulation alone. Subliminal antecedent stimulation of the same focus may yield extinction.[11,13] What is common in all these is that *antecedent stimulation* has so altered the functional condition of the CNS that the response to test stimulation is changed in the direction of *less* response. The antecedent stimulation must excite, and we would define as factors for extinction any changes of the CNS caused by antecedent excitation and causing a rise in threshold, an increase in latency, a decrease in amplitude or any combination of these.

In all that follows one must not confuse extinction—the diminution of motor response resulting from antecedent excitation of the parts of the CNS responsible for that same response—and inhibition, *i.e.* the diminution of motor response resulting from contemporaneous excitation in parts of the CNS responsible for an antagonistic response. Thus, though extinction and inhibition both result in diminution of motor response, inhibition depends upon reciprocal innervation, extinction does not.

METHODS

All experiments were performed on *Macaca mulatta* monkeys, fully anesthetized with Dial* (Ciba), 0.45 cc. per kg. bodyweight, half of the dose given intraperitoneally, half intramuscularly.

The duration of the electrical stimulations and the intervals between them were rigidly controlled by the timing-device previously described.[13] The pulses used to stimulate the cortex were either 60 ⌒ through a center-tap transformer grounded at its midpoint† or those of a Thyratron-stimulator after Schmitt and Schmitt,[36] permitting independent variation of the number of pulses per second (pattern-frequency), and the shape, or duration, of the individual pulses (pulse-frequency) as well as the voltage. These voltages are in this paper given in terms of the readings (in Ω) on a decade voltage-divider (VD) of 10,000 Ω.

The apparatus and electrodes used for the various purposes of the particular groups of experiments will be specified later. Suffice it here to say that for simple stimulation and for recording of the ordinary electrical activity of the various portions of the CNS regular stigmatic Ag-AgCl electrodes were used. In those cases in which "after-potentials" or

* We wish to thank the Ciba Co. for kindly putting the Dial at our disposal.

† A precaution to eliminate as much as possible polarization, kindly suggested by Dr. Hallowell Davis.

other slow components were studied special Agar-Ag-AgCl electrodes were used in combination with a D.C. amplifier and cathode ray oscillograph or with a Burr-Lane-Nims microvoltmeter.[8] The pH determinations were performed by a method previously described.[16, 17] The peripheral motor responses were recorded isotonically by tambours either on smoked paper or photographically with the cathode ray oscillograms.[31] The Agar-Ag-AgCl electrodes were made for us by Dr. L. F. Nims, who also gave his invaluable coöperation in those experiments in which pH was recorded.

The designation of the various areas of the sensorimotor cortex is that given in a previous paper.[14]

Results

Since both facilitation and extinction are changes in motor response, these can be observed only by comparing the response to *test* stimulation following *antecedent* stimulation with the response to test stimulation alone. This comparison presupposes that the physical properties of the test stimulus are constant, which depends upon constancy of the circuit both external to the animal and within the animal. This constancy has been established experimentally with a method previously described,[25] which permits determination of the instantaneous voltage and current through the specimen during stimulation.

A. *Necessity of Antecedent Neural Excitation*

In order to conclude that differences in response to constant test stimulation result from neural *excitation* it is necessary to exclude changes due

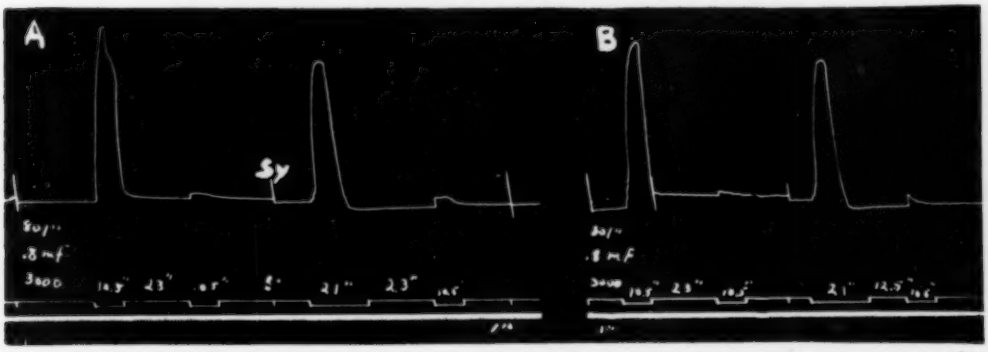


FIG. 1. Oct. 22, 1936. *Macaca mulatta*. Dial-narcosis. Record A shows 2 pairs of stimulations with all parameters the same, except that the antecedent stimulation in the 2nd pair is twice as long as that in the 1st pair. No increase in extinction. Record B repeats record A, except that the interval in the 2nd pair is half that in the 1st pair. Again extinction is not increased. Thus, whether one figures the effective interval as that between stimulations or that between responses, doubling the duration of the antecedent stimulation used here failed to increase extinction. In this and all subsequent figures, "sy" indicates synchronous points.

merely to the passage of the stimulating current. Gross changes of this nature were excluded indeed in experiments using the method above. Furthermore, the findings enumerated below are not explicable in terms of such changes: (i) motor response to cortical stimulation can be facilitated by

cutaneous stimulation (Bubnoff and Heidenhain); (ii) prolonged stimulation far enough below threshold does not produce facilitation or extinction; (iii) antecedent stimulation of such a duration that the response begins to decline before the end of stimulation produces as much extinction as does a stimulation twice as long (see Fig. 1); (iv) secondary facilitation, though present from widely separated foci in one subdivision of the sensorimotor cortex, is absent from near foci across the functional boundaries between leg-, arm- and face-subdivisions (see Fig. 2). This type of facilitation must obviously depend upon activity propagated transsynaptically, which is necessarily neural activity.

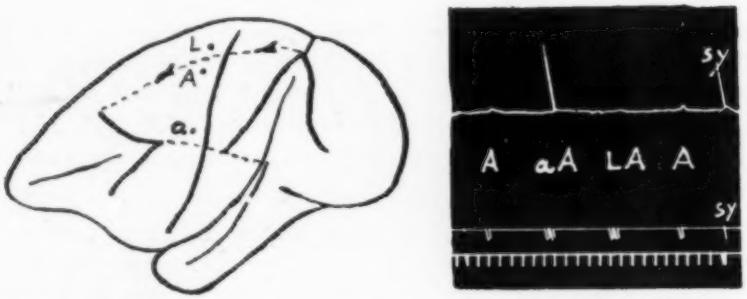


FIG. 2. Oct. 27, 1936. *Macaca mulatta*. Dial-narcosis. This figure shows the existence of secondary facilitation at A from a, 8 mm. apart, and the absence of facilitation across the functional boundary between the leg- and arm-subdivisions, although A and L are only 3 mm. apart.

From the above findings it is clear that observed differences in response, whether facilitation or extinction, cannot be referred to changes produced by *mere passage* of current of the antecedent stimulation, but must be referred to changes in the CNS resulting from neural excitation elicited by the antecedent stimulation.

B. *Multiplicity of Factors*

Some justification is required for speaking of factors for facilitation and factors for extinction instead of merely referring the two phenomena to increase and decrease of some single entity such as "excitability." Scrutiny of the following observations discloses the justification: (i) Facilitation and extinction can coexist.[9,10] If three equal stimulations are applied to one cortical "motor" focus in such temporal relation that the second and third both fall during the period of extinction induced by the first, but the third falls in the period of facilitation of the second, then the third response shows clear evidence of facilitation, though not as much as when the first stimulation is omitted (see Fig. 3); (ii) Facilitation by one criterion may concur with extinction by another. For example: a decrease in amplitude (extinction) may be associated with a decrease in latency (facilitation) (see Fig. 4); (iii) Facilitation of response to one type of test stimulation and extinc-

tion of response to another can be produced by a single type of antecedent stimulation (see Fig. 5).

It is difficult to conceive how this group of observations can be explained on the basis of changes in any *one* single parameter of nervous activity, *e.g.* in excitability. Nor is the difficulty solved, so far as we can see, by taking excitability as a variable, *i.e.* as being different at one time and place in the CNS from what it is at another. Thus we felt compelled to search for several

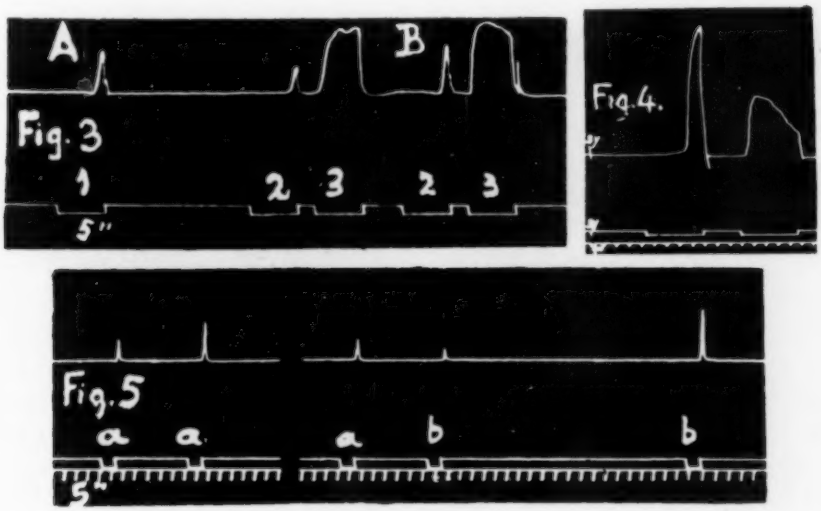


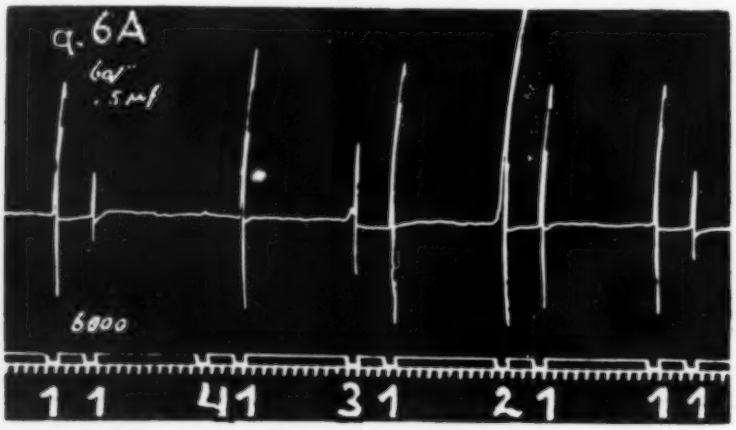
FIG. 3. Jan. 20, 1936. *Macaca mulatta*. Dial-narcosis. In record A three equal stimulations are applied to a "motor" focus. The response to stimulation 2 is extinguished, at this long interval, by the excitation set up by stimulation 1. The response to stimulation 3 is facilitated, at this short interval, by the excitation set up by stimulation 2. Record B shows the facilitation, at this interval, without extinction when stimulation 1 has been omitted.

FIG. 4. Oct. 16, 1936. The response to the second stimulation of a "motor" focus shows a shorter latency (facilitation) and a smaller amplitude (extinction) than the response to the first stimulation of this focus, *i.e.* dissociation of latency and amplitude.

FIG. 5. Jan. 31, 1935. *Macaca mulatta*. Dial-narcosis. Stimulation "a" facilitates response to "a", "a" extinguishes response to "b", as seen by comparing it with response to "b" alone.

factors for facilitation and extinction. That these factors had to be conceived as variables having different values at different times and places follows from the results of the following type of experiment, in which four stigmatic Ag-AgCl electrodes,—1, 2, 3 and 4,—are placed 1.5 mm. apart on a given "motor" area (*e.g.* Arm 4) on a straight line. Their positions have to be such that the primary movements obtained on monopolar stimulation of each of these four foci have an element in common, say extension of the wrist. It is then possible to investigate the effect of antecedent stimulation of focus 1, 2, 3 or 4 upon this common element of the response to test stimulation to focus 1 and thus to ascertain the spatial distribution of facilitation and extinction combined. By changing the interval between antecedent and

test stimulation one can thus study the intensity of facilitation and extinction as a function of space (the separation of electrodes) and time, or by



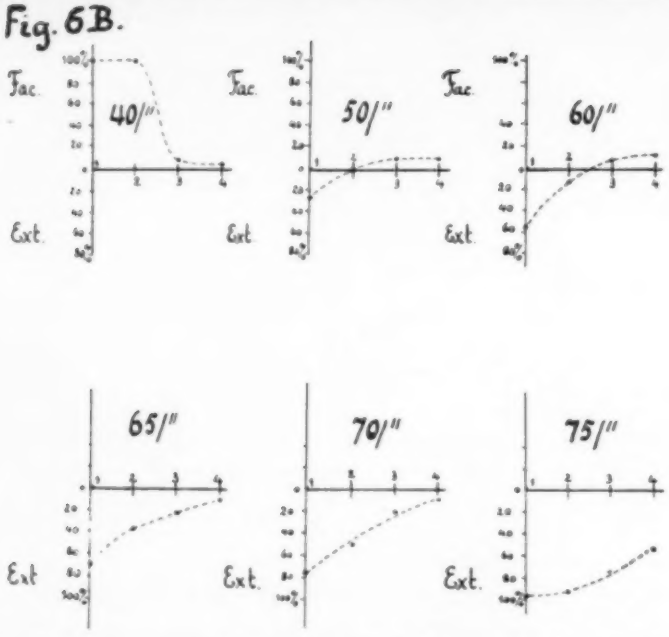


FIG. 6a. Feb. 21, 1935. *Macaca mulatta*. Dial-narcosis. Four stigmatic Ag-AgCl electrodes, 1.5 mm. apart, are so placed on a straight line on the "motor" arm area that the responses to stimulation of each of these foci have an element, extension of the wrist, in common. Record shows extinction from 1 on 1, equalization of response from 2 on 1, facilitation from 3 and from 4 on 1.

FIG. 6b. Same arrangement of electrodes as in Fig. 6a gives the average percentage change in size of many responses to test stimulation at focus 1 induced by antecedent stimulation at foci 1, 2, 3 and 4 respectively for various pattern-frequencies; all other parameters of stimulation and the interval between members of a pair being held constant throughout. At low frequencies pure facilitation in the vicinity of focus 1, at intermediate pattern-frequencies pure extinction around focus 1, facilitation at some distance (foci 3 and 4), at higher frequencies extinction from all foci, increasing as the frequency increases.

changing any of the parameters of stimulation, at constant interval, as a function of the separation of electrodes and the parameter varied. In the experiments of Fig. 6 the stimulations were at constant interval and the parameter varied was the pattern-frequency. On stimulation with lower pattern-frequencies facilitation was found greatest at focus 1 from focus 1, decreasing so as to be least at focus 1 from focus 4; with higher pattern-frequencies the same obtained for extinction. With intermediate pattern-frequencies extinction was found at focus 1 upon antecedent stimulation of near foci and facilitation upon antecedent stimulation of more distant foci. Figure 6A is an excerpt from a record with an intermediate pattern-frequency (60 per sec.); Fig. 6B shows diagrammatically this spatial distribution of facilitation and extinction combined as a function of the pattern-frequency of stimulation.

C. *Factors for Facilitation and Extinction*

The foregoing experiments have indicated the necessity of considering factors for facilitation and extinction, differing in kind and distribution. Inasmuch as these factors are functional changes in the CNS they can be disclosed only by examining what is going on *within* it. Since only changes in threshold and changes in activity can affect the response to test stimulation and since threshold and activity can both be affected by antecedent activity both must be investigated. Changes in the activity of any part of the CNS can be studied by recording the electrical activity of that part; changes in threshold of any part can be studied by determining the minimal electrical stimulation which produces an electrical response at that site.

It is essential to emphasize that, although these significant variables can be studied separately, they are inevitably interrelated in the living CNS. With impulses always impinging upon the part of the CNS under investigation a fall of threshold permits increased activity, increase of activity produces a rise of threshold. But that is not all. In peripheral nerve, changes in threshold have long been known to be associated with "after-potentials* and with changes in ion-concentration, notably phanges in pH. Therefore, in the following group of experiments the changes in activity and threshold were investigated by recording the electrical activity of various parts of the CNS, the threshold of the cortex, its "slow potentials"* and its pH before and after such electrical stimulation of the cortex as was shown to give facilitation or extinction of motor response to a particular test stimulation at a certain focus and after a given interval. It should be realized that in order to ascertain the altered electrical activity, "slow potentials" and pH of the cortex or other parts of the CNS at the time when the test stimulation would fall, this stimulation has to be omitted. Therefore, a separate, parallel experiment with antecedent *and* test stimulation has always to be made to ascertain whether, where and when facilitation or extinction obtains. With-

* For criticism of this designation see Discussion, below.

out both experiments it is impossible to infer what and how distributed in space and time are the functional changes underlying facilitation and extinction.

One of the conclusions from the experiments represented in Fig. 6 was that one obtained facilitation or extinction depending upon the distance of the locus of the test stimulation from that of the antecedent stimulation. This means that one has to investigate the changes mentioned above in the immediate neighbourhood of stimulation, at foci in the vicinity, at distant foci in the cortex and finally at other levels of the CNS.

1. *Changes in electrical activity*

a. *In the immediate neighbourhood of cortical stimulation.* Electrical stimulation of the cortex such as to produce profound extinction results in a temporary diminution or silencing of the electrical activity at the site and in its immediate neighbourhood.[29] For optimal localization of stimulation and recording of the activity at the site of stimulation it is necessary to use for both a single pair of concentric electrodes. We have employed concentric Agar-Ag-AgCl electrodes, the central electrode ending in a glass capillary 0.1 to 0.3 mm. in diameter and the circumferential circular electrode, between concentric glass tubes, about 6 mm. in diameter and 1 mm. wide.* Figure 7 shows a cathode ray oscillogram of the electrical activity of the cortex before and immediately following extinguishing stimulation under these conditions, the D.C. amplifier being disconnected from the specimen during stimulation. It will be noted that the electrical cortical activity following this extinguishing stimulation, although subthreshold in regard to motor response, is greatly reduced. With electrical stimulation apt to produce motor afterdischarge (long pulses, *e.g.* 60 ~) one is likely to find immediately after the stimulation, even when subthreshold in regard to motor response, a short period of electrical afterdischarge followed by a longer period of diminished electrical activity of the cortex. Figure 8 illustrates this statement. The form of the spikes in the discharge indicates (as will be discussed later) that it started in the cortex nearer the central electrode and ended under the circumferential electrode, so that at this stage facilitation was present around the area of extinction under the central electrode (a situation comparable to graphs 2 and 3 of Fig. 6B), whereas a little later the cortex underneath both electrodes had passed over into the stage associated with extinction.

b. *In neighbouring foci.* For recording of changes in electrical activity several millimeters away from the locus of stimulation but still in the cytoarchitectonic area of the same subdivision of the sensorimotor cortex two pairs of electrodes can be used, thus obviating difficulties of interpretation. The phases of afterdischarge and diminution of activity, corresponding to facilitation and extinction respectively, are more prolonged and often more

* These electrodes have been prepared for us by Dr. Nims and were found to be stable within 10μV.

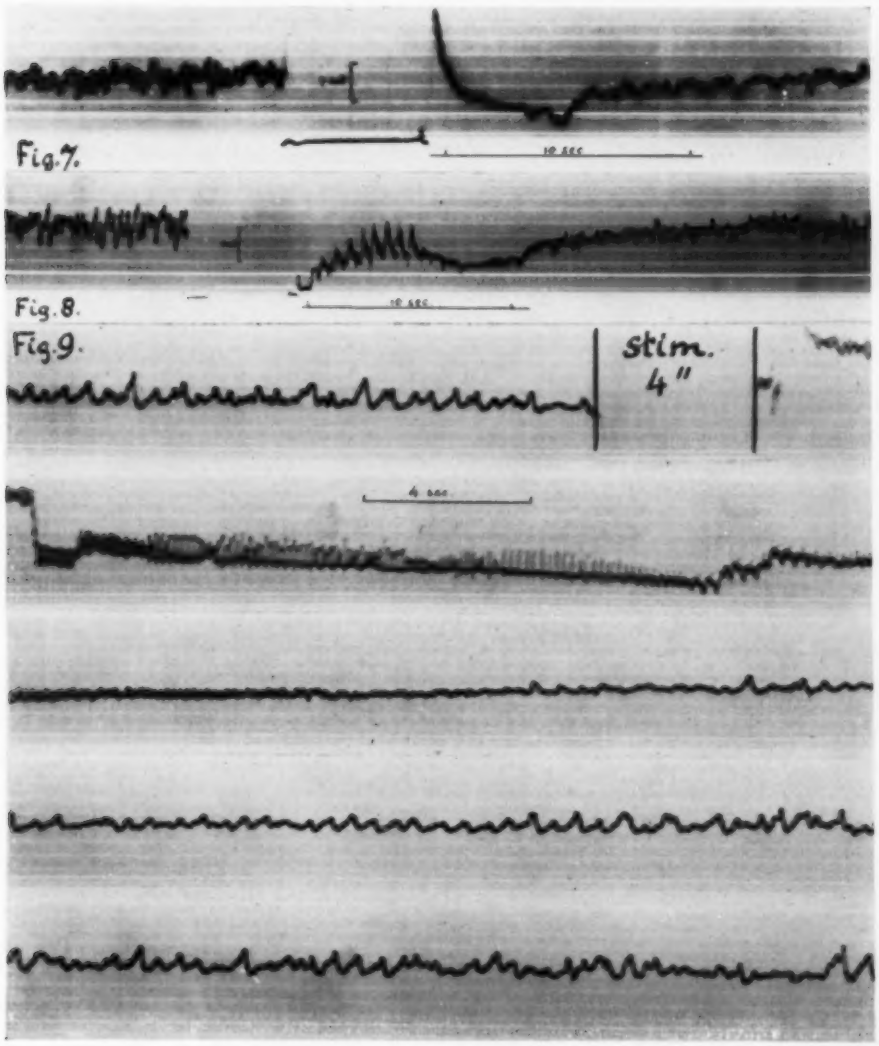


FIG. 7. Jan. 18, 1936. *Macaca mulatta*. Dial-narcosis. Cathode ray oscillogram of electrical activity of a focus of the "motor" arm area before and after electrical stimulation of this focus. Concentric Agar-Ag-AgCl electrodes used for stimulation and pick-up from a focus of motor arm area. Extinguishing subthreshold stimulation results in a very short-lived negative voltage drift followed by a positive drift and initial diminution of electrical activity of this focus. Lower heavy white line shows period of stimulation, upper heavy white line shows absence of peripheral motor response.

FIG. 8. Jan. 17, 1936. Same arrangement of stimulation and pick-up electrodes as in Fig. 7. This extinguishing stimulation (60 ⌣), known to give motor afterdischarge at or near threshold voltages, produced an initial electrical afterdischarge followed by diminution of electrical activity and gradual return to normal.

FIG. 9. Jan. 28, 1936. *Macaca mulatta*. Dial-narcosis. Cathode ray oscillogram of electrical activity of cortex before and after electrical stimulation. In this experiment two stimulating stigmatic Ag-AgCl electrodes were placed on dorsal portion of "motor" leg area (L.4) and parallel to them, 3.5 mm. distant, two similar pick-up electrodes on the ventral portion of the same area, thus minimizing voltage drifts. The subthreshold stimulation resulted in a marked prolonged electrical afterdischarge followed by diminution of electrical activity (extinction) with gradual return of it to normal. (Continuous record.)

pronounced. An example is supplied in Fig. 9 in which it will be seen that, following the electrical stimulation of a focus of L.4, the electrical activity of a focus of the same area 3.5 mm. distant is at first greatly increased—electrical afterdischarge—then diminished to return to normal about a minute after stimulation.

c. *In more remote parts of the cortex.* Under this heading comes the description of the changes in electrical activity in various cytoarchitectonic

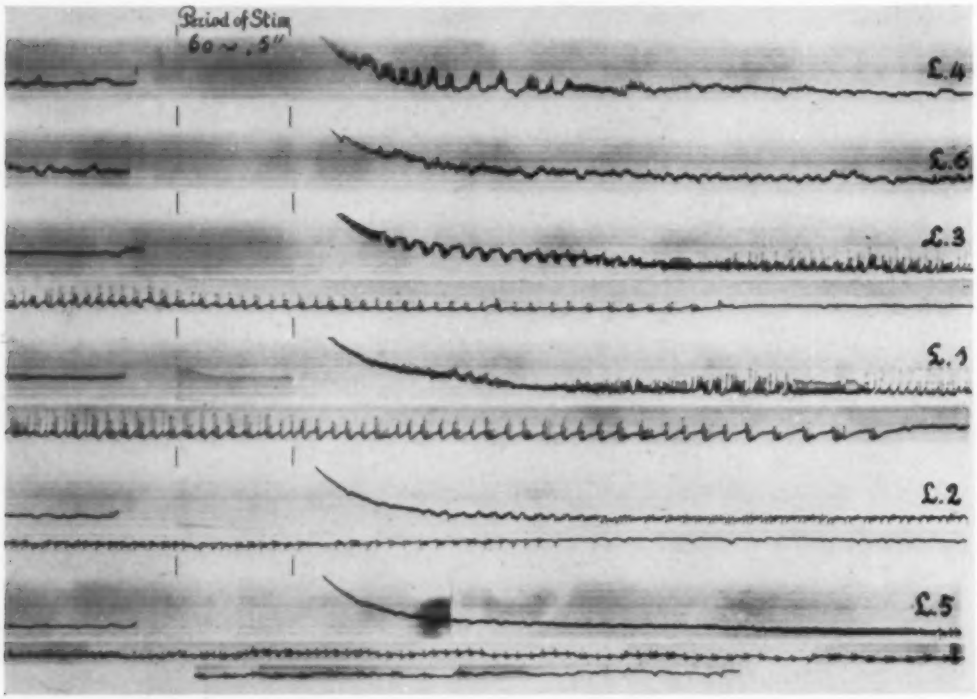


FIG. 10. April 23, 1936. *Macaca mulatta.* Dial-narcosis. Cathode ray oscillograms of electrical activity of various foci of the leg-subdivision of the sensorimotor cortex. In each of the records of this figure L.4 was stimulated (60 ~, 5 sec.) with bipolar Ag-AgCl electrodes and the electrical activity recorded with similar electrodes from the named areas successively. For further comments see text.

areas of one subdivision upon stimulation anywhere within this subdivision. With one pair of stimulating electrodes always on, let us say, L.4 the electrical activity of another locus in this area and of associated areas of this subdivision (L.6, L.3, L.1, L.2 and L.5) was recorded successively before and after stimulation. Figure 10 shows the changes in electrical activity in these various leg areas following stimulation of L.4. In the particular experiment to which Fig. 10 relates the pick-up electrodes were so arranged that those in the leg areas were successively connected to the grid of the amplifier, the cathode being simultaneously connected to an electrode in the corresponding area of the arm-subdivision. This arrangement allowed

one to interpret the sign of the recorded deflections in terms of the site and direction of propagation of the electrical activity in the leg-subdivision, since the activity of the arm-subdivision was not influenced by the stimulation of L.4.

In an experiment of this kind with a D.C. amplifier and intended to record slow "D.C. potentials," the usual procedure of placing one of the electrodes as a reference-electrode on a killed portion of the cortex is inappropriate on account of the spurious slow potentials produced.

Examination of Fig. 10 reveals the following: a. subliminal stimulation of L.4 results in electrical afterdischarge not only in L.4, but also in L.3, L.1, L.2 and L.5, not in L.6—a distribution of hyperactivity in entire harmony with the functional organization of the cortex as revealed by local strychninization;[14] b. comparison of the pictures of after-discharge in L.4 and L.3 shows that the sign of the rapid potential fluctuations in L.4 is always in the same direction (upwards = negative), whereas the fluctuations in L.3 are initially of the opposite sign, then suddenly reverse. So far as we can see there is only one possible interpretation, compatible with our analysis of the strychnine-spike,[15] namely that negative swings and negative spikes express activity originating in the area itself with the superficial layers leading, whereas the positive swings with positive spikes indicate activity with the deeper layers leading. This interpretation is furthermore in harmony with the findings and interpretations of Bishop and collaborators,[2,3,4,5] of Marshall, Woolsey and Bard[26,27] and of Adrian.[1] This indicates that L.4, which was stimulated electrically, is itself in active discharge immediately after this stimulation, whereas L.3 at first receives impulses from L.4 resulting only after more than 10 sec. in an active discharge of the area itself. Essentially the same can be seen in the other records of the postcentral areas and it is of interest to note that the active phase of the discharge begins later and ends later the more remote the area from L.4.

In these experiments sub C 1, a, b and c the period of electrical afterdischarge is regularly followed by a period of electrical inactivity, as can be seen from Figs. 8 and 9. This phenomenon is not obvious in Fig. 10 because the animal was deeply narcotized and the amplification used was purposely small to insure full recording of the spikes of the after-discharge.

d. *In distant parts of the CNS.* Associated changes in electrical activity can be observed in other portions of the CNS, *e.g.* the spinal cord.[29] In Fig. 11 is shown the electrical afterdischarge in the white matter of the lumbar enlargement (ventrolateral column) of a monkey's cord following electrical stimulation of a focus of the cortex of L.4. These four records were made with increasing voltage of stimulation, the last being just supraliminal. Figure 12 is a record of the electrical activity of the grey matter (ventral horn) of the cervical enlargement of the cord before and after subliminal electrical stimulation of a cortical focus of A.4. Comparison of these two typical records shows that while the afterdischarge in the white matter resembles that obtainable from the cortex, the picture from the grey matter differs, in that

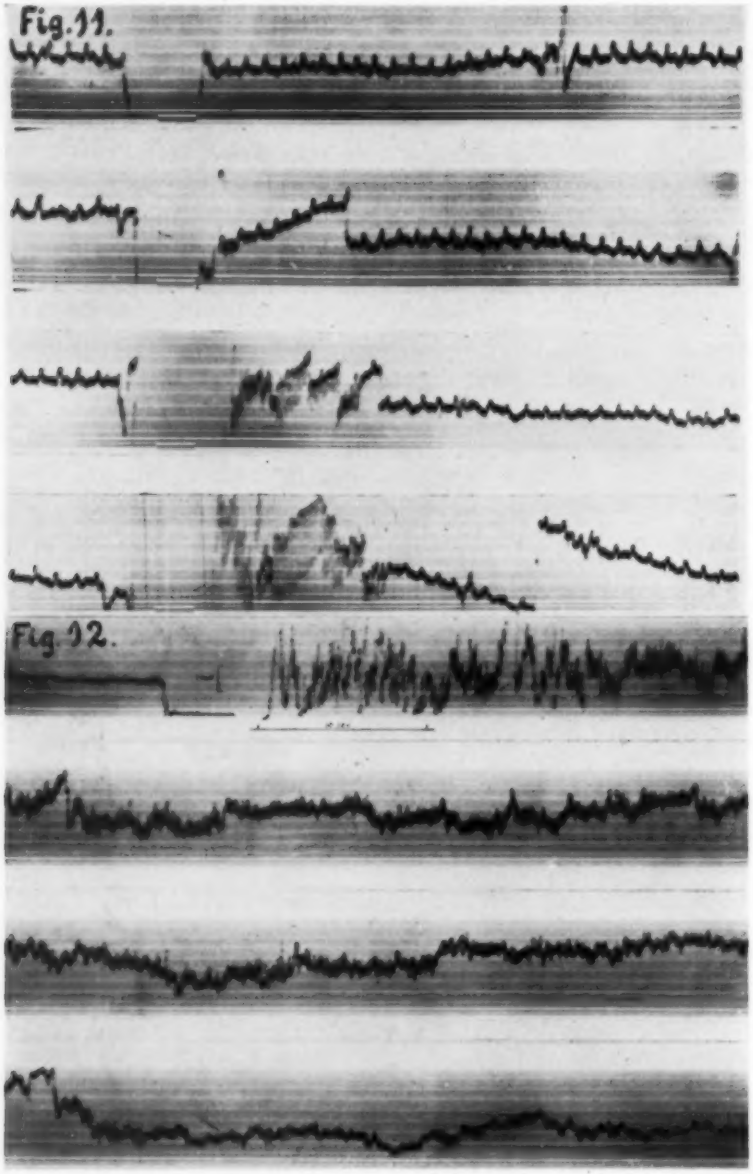


FIG. 11. Jan. 29, 1936. *Macaca mulatta*. Dial-narcosis. Cathode ray oscillograms of electrical activity of ventrolateral column of lumbar enlargement of spinal cord before and after electrical stimulation (60 ⌒, 4 sec.) of contralateral motor leg area (L.4). Strength of stimulation in record 1 = 2000, in record 2 = 3000, in record 3 = 4000, in record 4 = 6000. The last stimulation was just supraliminal (see upper heavy white line in 4). Note voltage drifts so great as to require balancing of spot on screen of cathode ray oscillograph. Lower heavy white line in all records shows period of stimulation.

FIG. 12. Jan. 20, 1936. *Macaca mulatta*. Deep Dial-narcosis. Cathode ray oscillogram of electrical activity of ventral horn of eighth cervical segment of spinal cord before and after bipolar subthreshold stimulation of focus of contralateral "motor" arm area (A.4). Note the prolonged electrical afterdischarge in grey matter of cord. Under this deep narcosis extinction lasted more than 5 min., less than 10 min. (Continuous record.)

it is more irregular and much more prolonged. Once these changes in electrical activity following one period of stimulation of the cortex were known, their relation to facilitation and extinction could be investigated by applying at an appropriate interval a second, or test, stimulation. During the early stages of afterdischarge in a "motor" area (*e.g.* A.4) induced by stimulation of this area itself or of a remote related area (*e.g.* A.5) test stimulation to this "motor" area (A.4) results in a facilitated motor response, whereas during the later stages of afterdischarge this test stimulation elicits a smaller or no motor response (extinction) and even frequently terminates the existing afterdischarge. The motor response to test stimulation applied during the period of electrical inactivity of the cortex following an electrical afterdischarge is always extinguished.

2. *Slow voltage drifts*

When records of the electrical activity of the cortex before and after stimulation are taken with a direct-coupled amplifier the site of stimulation is seen to be negative at the end of stimulation and to become slowly positive with respect to a distant focus. These slow drifts appear with almost any type of electrode. With due precautions as to the type of electrodes and circuits used for pick-up and stimulation these changes can be shown to be not artifacts but physiological phenomena. To observe these changes as precisely as possible at the site of stimulation requires again that a single pair of concentric electrodes be used both for stimulation and pick-up. Obviously for such an experiment the electrodes must be non-polarizable; as such we used the concentric Agar-Ag-AgCl electrodes mentioned above, which in practice were found to be good to some 4 or 5μV. It was with these electrodes that the record of Fig. 7, showing the negative (up) and positive (down) slow drifts at the site of stimulation, was obtained. For investigation of slow drifts at foci other than that stimulated separate pairs of electrodes for stimulation and pick-up can be used. This in itself obviates one of the possible sources of artifact, *i.e.* alteration of the pick-up electrodes by passage of the stimulating current. Moreover, one can use for stimulation a transformer, with a center-tap grounded and permanently connected to the cathode of the amplifier. For foci near the site of stimulation one of the pick-up electrodes, to wit, the "live" electrode, can be placed half-way between the two stimulating electrodes and connected to the grid of the amplifier, except during stimulation when it must be disconnected. The reference-electrode, placed on a distant unrelated cortical focus (*i.e.* one not affected by the stimulation) is connected permanently with the cathode of the amplifier, ground and the center-tap of the transformer. This circuit is so symmetrical as to be practically free of D.C. artifacts, except for a slight shift produced by rectification of the A.C.-current in the transformer. The slow voltage drifts recorded in this way are essentially similar to those already described; they are somewhat larger and more complicated by action potentials due to the greater separation of the electrodes. Moreover,

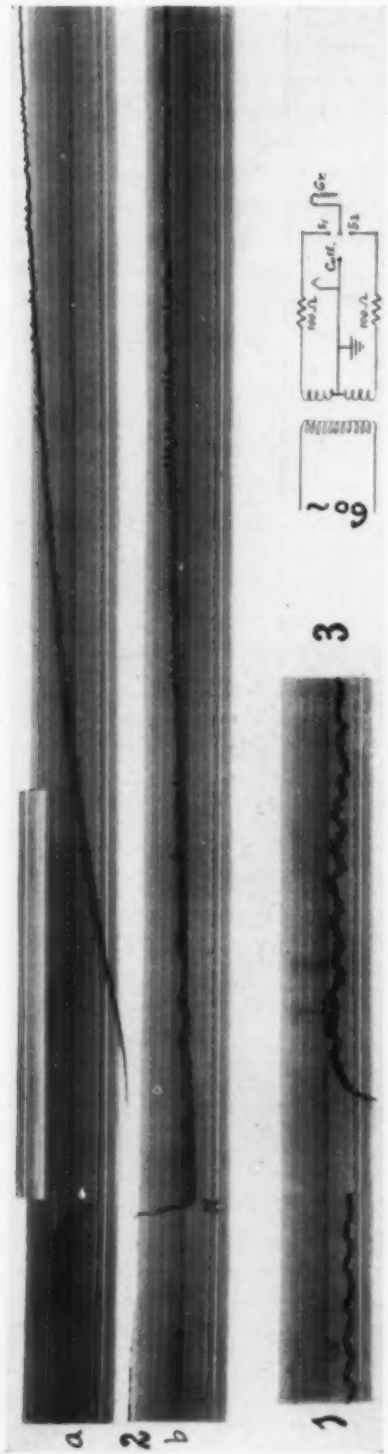


FIG. 13. April 16, 1936. *Macaca mulatta*. Dial-narcosis. Record 3 shows arrangement of four electrodes (Agar-Ag-AgCl) on cortex and their connections to the center-tap transformer, and to the cathode, ground and grid of the amplifier. Record 1 shows the electrical activity and the small and short-lived negative (down) and positive (up) voltage drifts following liminal stimulation (4 sec., 60 ∽) of a focus of the motor arm area (A.4) in the lightly narcotized animal. Record 2 shows the marked and prolonged negative and positive voltage drifts following liminal stimulation (4 sec., 60 ∽) of the same focus when the animal was deeply narcotized. Sections a and b of record 2 continous. The insert in this record shows the interval at which equalization of threshold response occurred in this stage of narcosis. x = balancing of spot on screen.

inasmuch as the "live" lead is not exactly at the site of stimulation, they never show the complete inactivity (extinction) revealed with a single pair of concentric electrodes. Figure 13[3] shows diagrammatically the connections of the center-tap transformer and the amplifier to the four electrodes on the cortex. Figure 13[1] and 13[2] were obtained on the same animal, in both cases with liminal 60 ~ stimulation. Figure 13[1] was obtained in the lightly narcotized monkey when facilitation lasted only a few seconds, whereas Fig. 13[2] was recorded under deep narcosis. It will be seen that in the latter case the stimulation is followed by a very marked negativity (downward) succeeded by a long lasting positivity (upward), so great as to require balancing of the spot on the screen of the cathode ray oscillograph at the point

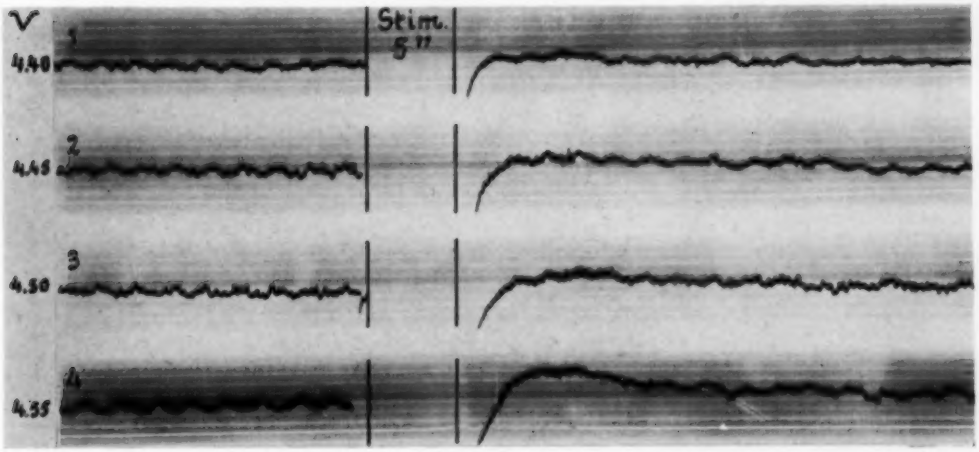


FIG. 14. April 15, 1936. *Macaca mulatta*. Light Dial-narcosis. These cathode ray oscillograms show the gradual increase of electrical afterdischarge and negative and positive voltage drifts with increase of stimulation of a focus of A.4. All stimulations (4 sec., 60 ~) the same except for voltage. Arrangement of electrodes as in Fig. 13. With these strengths of stimulation facilitation lasted as long as the periods of fast action potentials of these records. Voltages (V) at left of records.

marked x. On Fig. 13[2a] is an insert, from a record of a parallel experiment and taken with the same speed of paper, showing the interval at which repetition of the stimulation yields equal motor response. It will be observed that this happens at a time between the negativity and positivity when the voltage is practically zero. At all intervals shorter than this "equalization" interval facilitation of motor response was encountered; outside this interval for a period of many minutes, *i.e.* much longer than the record represents, total extinction of motor response obtained. Thus "negativity" is associated with facilitation, "positivity" with extinction. These voltage drifts are sufficiently prolonged to admit recording with a microvoltmeter[8] and an ordinary sensitive galvanometer, and by this method their sign and magnitude are found to be as indicated. Since the period of such a galvanometer is relatively long it distorts the time-relations and for this reason no such record is presented.

Such a simple association of these voltage drifts with facilitation and extinction is found only when electrical afterdischarge is avoided by proper selection of the stimulation. With afterdischarge, which during its stage of rapid discharge has been shown above to be a factor for facilitation, the period for facilitation is prolonged into the period of positivity. In the particular experiment of Fig. 14 wherein the afterdischarge had only a fast phase, the facilitation lasted as long as the afterdischarge, whereafter extinction, even to stronger test stimulation, ensued. Figure 14 demonstrates the changes in electrical activity and the slow drifts following four stimulations of a focus of A.4 at various voltages through capillary Agar-Ag-AgCl electrodes of high resistance. It will be seen that with gradual increase of the stimulating voltage the electrical afterdischarge and associated drifts become more pronounced. In all cases there was a motor afterdischarge of very small amplitude, though to the first two stimulations (records 1 and 2) there was no visible primary response.

It should be mentioned here that when an electrical afterdischarge is propagated into a remote area related to the one stimulated, this remote area at first "climbs" negative, and then, as it begins to discharge actively, "climbs" positive in respect to an unaffected reference-area, and when electrical inactivity ensues it is and remains for some time on the positive side. This means that the activity of a given area has the same effect on its slow voltage drifts regardless of how this activity was initiated, *i.e.* whether by direct electrical stimulation or by a disturbance propagated into it transsynaptically.

3. *Changes in pH of the cortex*

It has been shown so far that facilitation is associated with increased electrical activity and a negative voltage drift, extinction with decreased electrical activity and a positive voltage drift. These factors are sufficient to account for the period of facilitation, the time of equalization of motor response and the beginning of extinction. It was found, however, that the positive voltage drift disappeared before the electrical activity of the cortical focus returned and before extinction had passed off. Investigation of the latter part of the period of extinction showed that the end of extinction coincided with the return of normal electrical activity. The question then arose, what factor underlies the terminal portion of the period of electrical inactivity and associated extinction? Obviously this must be a change in threshold. Several old and new observations had pointed toward the pH as a significant variable in determining the activity of the nervous system, more particularly in determining the threshold of isolated nerve. Moreover, it was only reasonable to assume that the increased activity of the cortical cells stimulated would eventually lead to an increased production of acid metabolites. These considerations themselves were sufficient to necessitate pH-determinations of the cortex under various conditions of activity. For-

tunately this demand could be met, since the glass-electrode technique of pH-determinations had been developed sufficiently by Nims to be applicable to determinations *in vivo* and had been already used by him in collaborations with the authors in investigations on the effects of intravenous injections of acids, alkali and changes in ventilation on the pH of the cortex and the corresponding changes of its threshold.[16,17] In the second paper cited it was stated that a change of pH of the cortex from 7.3 to 7.5, however induced, resulted in a decrease of more than 25 per cent of the voltage required to initiate a minimal electrical afterdischarge, and that a decrease of pH to 7.1 raised the threshold much more than proportionally. In the same paper will be found evidence to the effect that hyperactivity of the cortex, whether due directly to electrical stimulation or to an afterdischarge propagated into an area investigated, causes a large decrease of pH which cannot be referred to anything but the increased activity of the nerve cells involved, and, finally, that this "acidity" persists as long as the prolonged diminution in electrical activity of the cortex and its concomitant rise in threshold[17] (pp. 286 and 287). In Fig. 7 of that paper an initial alkaline wave, beginning during stimulation, will be seen. At that time we were not certain that this wave might not be an artifact, although it was constantly present with all effective stimulations, regardless of the distance of the pH electrodes from the stimulating electrodes and notwithstanding all possible precautions to make the stimulating current symmetrical and the stimulating and recording circuits as independent as the requirements of the experiment permit. It was not until we had evidence of the association of an alkaline wave in the cortex with the rapid phase of a central electrical discharge, induced by convulsant drugs in the curarized animal,[18] that we were convinced of the significance of the observed initial alkalinity. Since this alkalinity coincides with the early part of the period of negative voltage drift it is impossible to observe the influence of this alkalinity by itself upon cortical threshold and motor response; one can only infer from the observed effect of cortical alkalinity otherwise induced that it must give a fall in threshold of all nerve cells in the "alkaline region" and so operate as a factor for facilitation.

Figure 15 presents diagrammatically the relation of facilitation and extinction of motor response induced by 60 ~ stimulation of a "motor" focus to the corresponding changes in electrical activity, voltage drifts and pH at the site of stimulation.

To summarize the results of the experiment sub C one can say 1. that increased activity, negative voltage drift and alkalinity operate as factors for facilitation; 2. that decreased activity, positive voltage drift and acidity operate as factors for extinction. The distribution of these factors in the CNS, both as regards time and place, is determined by the propagation of neural impulses from the site of initial stimulation, the increased activity in remote areas determining in them slow voltage drifts and changes in pH.

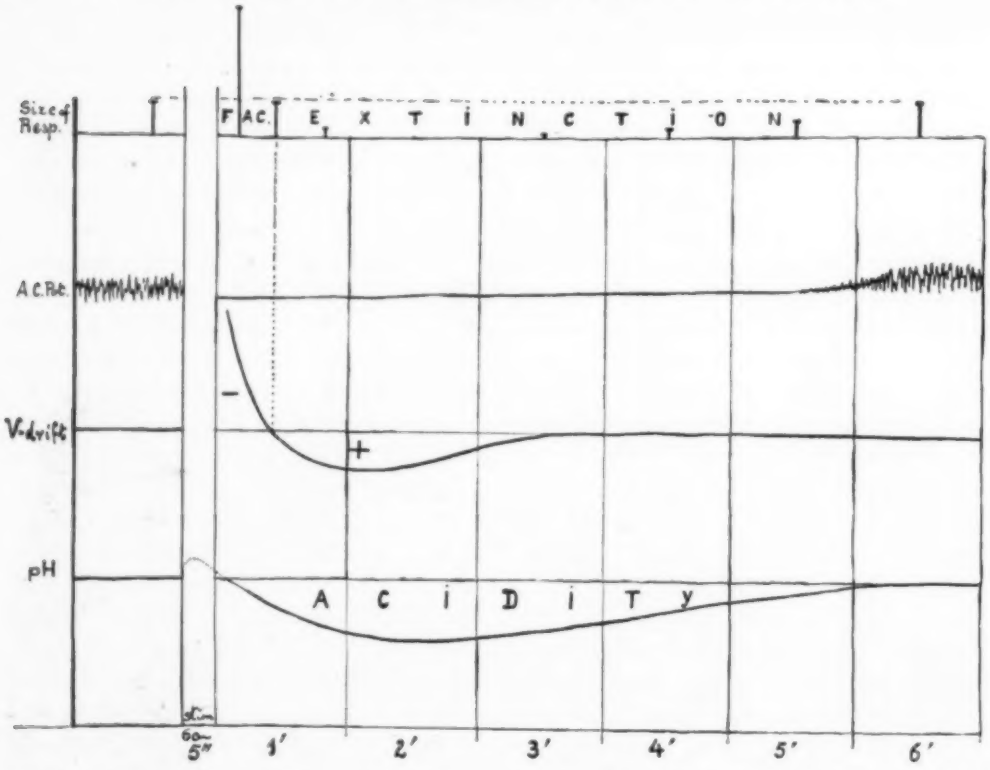


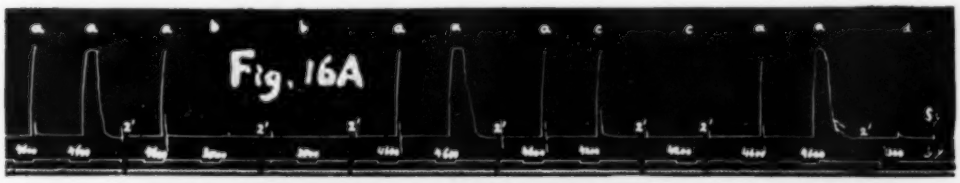
FIG. 15. Diagram of correlation of facilitation and extinction with changes in electrical activity, voltage drifts and pH at the site of stimulation.

D. *Mode of Action of Factors for Facilitation and Extinction*

From general considerations of a host of observations, old and new, of many investigators it seems permissible to infer that the mode of action of these three kinds of factors is as follows: 1. changes in activity as such alter the amount of summation to be expected at subsequent synapses; 2. slow voltage drifts are either the electrical manifestation of changes in temporospatially dispersed activity (*i.e.* action potentials which overlap and sum to give a smooth contour) or changes in voltage of cells that have been discharged (*i.e.* "after-potentials") or a mixture of these; 3. changes in pH involve all nervous structures lying within the region of altered pH, and thus involve cells that have not yet been discharged. These implications are of direct interest in connection with many of the problems pertaining to facilitation and extinction. First let us consider the dissociation of changes in latency and in amplitude, as exemplified in Fig. 4, where decrease in latency (facilitation) is associated with decrease in amplitude (extinction). To account for the decrease in latency of a response one must assume that less summation is required, *i.e.* that there is a fall in threshold to repetitive stimulation, whereas to account for the decrease in amplitude one must assume that fewer nerve cells are capable of responding.

1. *Relation of latency and threshold*

If the first of these assumptions is correct one must expect that stimulations giving facilitation with decrease in latency but with little or no change in amplitude will produce a marked fall in threshold of the focus under investigation. That this is so can be seen in Fig. 16. In this particular experiment the threshold was slightly below 4300, and 4200 was definitely subthreshold, yet the response to it as test stimulation was as large as the response to the antecedent stimulation at 4600. Even test stimulation at 3500, *i.e.* following a stimulation at 4600, brought in a just visible response. Figure 16A, therefore, shows that some cells of the nervous structures involved



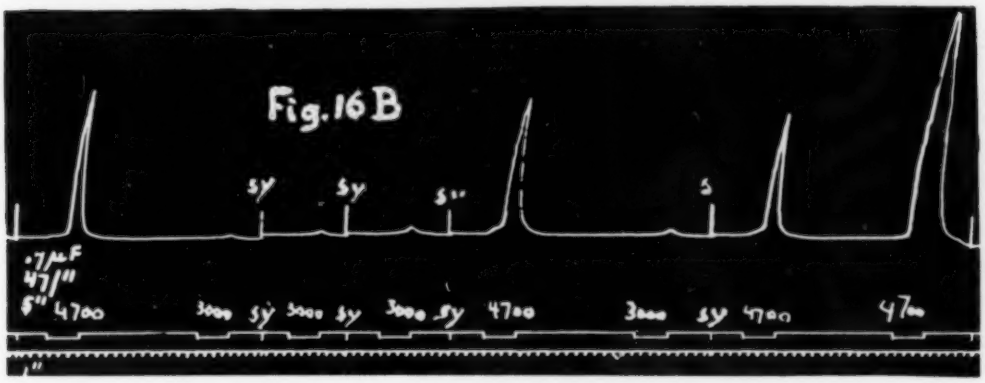


FIG. 16A. Dec. 1, 1938. *Macaca mulatta*. Dial-narcosis. This figure shows that facilitation as judged by decrease of latency is associated with a marked fall of the voltage threshold.

FIG. 16B. March 10, 1939. *Macaca mulatta*. Dial-narcosis. This figure shows constancy of threshold with constancy of latency accompanied by marked increase of amplitude (see last two responses).

have been rendered excitable to voltages formerly far subthreshold. It is even possible to dissociate latency and amplitude in the opposite direction, *i.e.* to obtain facilitation as judged by increase of amplitude without change of latency or even with a slight increase of latency (see Fig. 16B). Under these conditions there is no obvious change or a slight rise in voltage-threshold. Taken together these findings show that latency and voltage-threshold are covariant regardless of amplitude. Amplitude of response must, therefore, depend upon some factor other than threshold; this must be a change in activity available for summation.

2. *Dissociation of latency and amplitude of motor response*

The second assumption, namely that during extinction, as judged by decreased amplitude, fewer cells are capable of responding, implies that these cells have passed over into a period of extinction, and this, in turn, that with pairs of equal stimulation the amplitude should decrease with increase of interval because cells previously active or in the period of lowered threshold (negative voltage drift) will now have passed into the period of raised threshold (positive voltage drift), even when the decrease of latency is not yet materially affected by the increase of interval. That this is the case is seen in Fig. 17. This figure shows a series of eight pairs of equal stimulations with gradually increasing intervals and so exhibits the latency and amplitude of the second response as a function of the interval. It will be seen that the latencies of the second responses are smaller than those of the first in graphs a, b, c and d, equal in e, and greater in f, g and h, though the amplitude of the second responses is decreased in *all* graphs, *i.e.* the amplitude falls off earlier than the decrease in latency.

It should be noted that between each graph of Fig. 17 there was a pause of 2 minutes. The variations in size of the first responses are the expression of the waves of cortical excitability previously described.[6, 23]

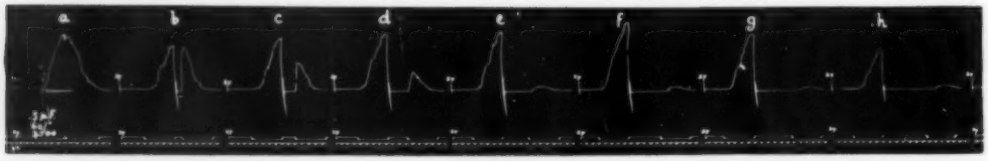


FIG. 17. Oct. 16, 1936. *Macaca mulatta*. Dial-narcosis. This figure shows the dissociation of latency and amplitude in the response to constant test stimulation as a function of the interval after constant antecedent stimulation. Intermission between pairs = 2 min. Stimulus selected to avoid afterdischarge.

Thus in the first half of Fig. 17 one has an admixture of facilitation and extinction, in the latter half pure extinction, *i.e.* by both criteria. In order to obtain such a record one has to use relatively long stimulation and one not giving cortical afterdischarge, so that at the end of it many nerve cells have been discharged so often as to suffer the rise in threshold associated with positivity. In graph a, with an interval of only 0.2 of a second, the response to the second stimulation is practically a continuation of that to the first and declines during stimulation. Such a pair of stimulations may well be regarded as a single stimulation of double duration, the response to which exhibits extinction during stimulation. To account for this, one has to suppose that all the nerve cells which stimulation at this site, of this voltage and this wave form (pulse-frequency) can reach have become inexcitable to it. At such a time a response can still be elicited by stimulation of higher voltage or longer wave form (lower pulse-frequency), but not by one with higher pattern-frequency. Here it is important to point out a similarity to

peripheral nerve, in that, so long as afterdischarge is avoided, there exists for cortical stimulation a maximal stimulus in terms of change of any one parameter of stimulation except the voltage. The experiment just cited (Fig. 17) exhibits the justification of this statement in regard to the duration of stimulation. The exception concerning the voltage depends obviously upon the limited number of fibers in a peripheral nerve, whereas in the case of the cortex a higher voltage with consequent wider spread of current will always find more remote cells hitherto uninvolved.

3. *Influence of parameters of stimulation*

In a previous paper, dealing with pairs of equal stimulation, it was pointed out that, other conditions being equal, an increase in the total energy of stimulation by increase of any one of its parameters (duration, voltage, pattern-frequency or pulse-frequency) gave increase extinction[13] (p. 520). In that same paper it was further stated that with pairs of *unequal* stimulations the change in size of the motor response to the test stimulation is determined by each and every one of the parameters of both the antecedent and the test stimulation, as well, of course, as by their interval.

Though we cannot as yet show the relation of each of these nine variables to the temporo-spatial distribution of the three known factors for facilitation and extinction, we have now to present some findings in such experiments with pairs of unequal stimulations.

a. *Pairs unequal in duration only.* In the experiment of Fig. 18A four pairs of stimulations, the interval between members of each pair being 15 sec., were

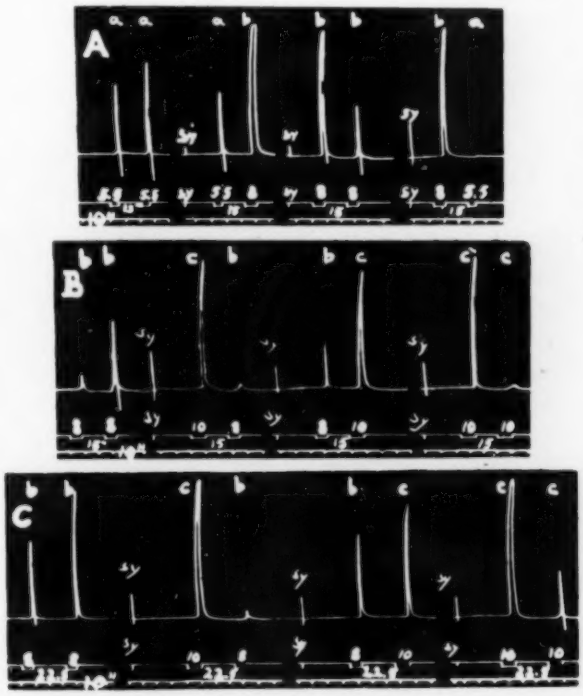


FIG. 18. Dec. 2, 1938. *Macaca mulatta.* Dial-narcosis. Each record contains four pairs of stimulations, differing only in duration. Unchanged parameters of these stimulations: 40/″; .5μF; VD = 2150. The interval between members of each pair was in records A and B 15 sec., and in record C 22.5 sec. The durations in record A were 5.5 and 8 sec.; in records B and C, 8 and 10 sec. Note in record A that "a" facilitates "a" and "b", "b" extinguishes "b" and "a". In record B, "b" facilitates "b", facilitates "c" as to latency, extinguishes it as to amplitude, "c" extinguishes "b" and "c". In record C it will be seen that "b" facilitates "b", but extinguishes "c", while "c" extinguishes both "b" and "c".

given. It will be seen that the shorter stimulation, "a", always produced facilitation, the longer, "b", always extinction; for the unaffected size of the response to "b" see responses 5 and 7. From this series it might seem as if the duration of the test stimulation is not significant; however, from Fig. 18B, where longer stimulations (8 and 10 sec. respectively) were used, it will be seen that the duration of the test stimulation must be considered. While the long stimulation, "c", extinguishes both the response to itself, "c", and to the short stimulation, "b", and this stimulation, "b", facilitates the response to itself, "b", it produces a mixture of facilitation (shorter latency) and extinction (lesser amplitude) of the response to stimulation "c". Records A and B were taken with the same interval (15 sec.) between members of each pair of stimulations.

In Fig. 18C, with the same type of stimulation as in Fig. 18B, but with the interval increased to 22.5 sec., it will be seen that now the effect of "b" on the response to "c" is extinction with regard to both latency and amplitude. The differences in results of Figs. 18B and 18C are in entire harmony with those of Fig. 17, showing the relation of the interval to the dissociation of latency and amplitude of the second response. The results of Fig. 18A and 18B, due to difference in duration of the stimulations ("a" and "b" versus "b" and "c"), are to be expected because the shortest of these, "a", is such as to give predominantly facilitation, whereas "b", being longer, produces somewhat more extinction, thus resulting in the admixture of facilitation and extinction (see Fig. 18B, pair "bc"), present also in Fig. 17.

In records like that of Fig. 18C, where one pair of stimulations produces one result and the other three the opposite, one is forced to conclude that the altered parameter of stimulation is significant in both antecedent and test stimulation. In the experiment of Fig. 18C it was the change in duration; in the subsequent Fig. 19, 20 and 21 the same will be shown for each of the other parameters.

b. *Pairs unequal in pattern-frequency only.* In experiments like the one depicted in Fig. 19 the only difference between the members of a pair of

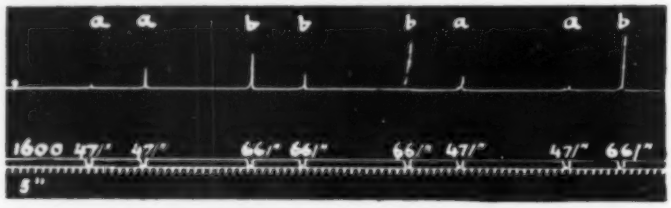


FIG. 19. Feb. 12, 1935. *Macaca mulatta.* Dial-narcosis. This figure illustrates the effect of change in pattern-frequency alone. "a" facilitates "a" and "b"; "b" facilitates "a", but extinguishes "b".

stimulations was in the number of pulses per second (pattern-frequency). By suitable selection of all parameters of the two stimulations and their interval it is possible to find such stimulations that those of lower pattern-

frequency produce facilitation of response to themselves and to those of higher frequency, whereas those of higher pattern-frequency facilitate responses to those of lower frequency in spite of the fact that they produce extinction to themselves.

That in the pair "ba" the response to "a" is facilitated is clear by comparing this response with the first and seventh responses, which are unaffected by antecedent stimulation. This relation of these responses shows that the pattern-frequencies of both antecedent and test stimulation are significant.

c. *Pairs unequal in pulse-frequency only.* Figure 20 represents an experiment in which only the pulse-duration is altered. The stimulation with longer pulses, *i.e.* of lower pulse-frequency, always extinguishes, whereas stimulation with shorter pulses, *i.e.* of higher pulse-frequency, while it facilitates the response to itself, extinguishes the response to the stimulation of lower pulse-frequency.

That in the pair "ab" the response to "b" is extinguished is clear by

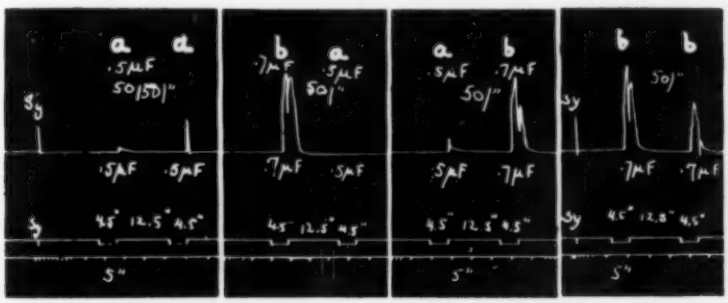


FIG. 20. Feb. 21, 1939. *Macaca mulatta.* Dial-narcosis. This figure demonstrates influence of change in pulse-frequency alone. "a" facilitates "a", but extinguishes "b"; "b" extinguishes "a" and "b".

comparing it with the third and seventh responses, which are unaffected by antecedent stimulation. Looking at this figure it is at once apparent that when all other parameters of stimulation are held constant, that having the lower pulse-frequency produces the larger response, *i.e.* that more motor-units have been excited. This presumably means that more cortical cells have been excited, rather than that a given group has been excited more often, for the pattern-frequency and duration of the stimulation were held constant. Since this experiment was made at constant voltage also, the voltage-gradient at any point in the cortex remains constant from stimulation to stimulation. Therefore, the increase in response with decrease of pulse-frequency is presumably due to an increase in the percentage of nerve cells excited within the area having a given voltage-gradient, rather than to any increase of that area. If this conception is correct, it must mean that the longer pulse-form excites a larger percentage of the cells by inclusion of cells with higher threshold. This is borne out by the comparatively slight effect of shorter

pulses upon the responses to longer pulses, and the dominance of stimulation with longer pulses; for these can excite all the cells which the short pulses had excited, certainly if their threshold were lowered and even if it were somewhat raised. On the other hand it also implies that with longer pulses which can excite the vast majority of the nerve cells the decrease of excitability of a few of these will be sufficient to exhibit decrease of amplitude of response (extinction), whereas with shorter pulses there always remain enough nerve cells available for increase of amplitude of response (facilitation) even though many cells originally discharged have become inexcitable to these or longer pulses. Thus it should be possible to find a stimulation of shorter pulse-form which, though it produces facilitation of response to an equal test stimulation, produces extinction to test stimulation of longer pulse-form, as shown indeed in Fig. 20. Compare again the facilitation in record 1 and the extinction of response to "b" by "a" in record 3 using the response to "b" in record 2 or the first response to "b" in record 4 as standard.

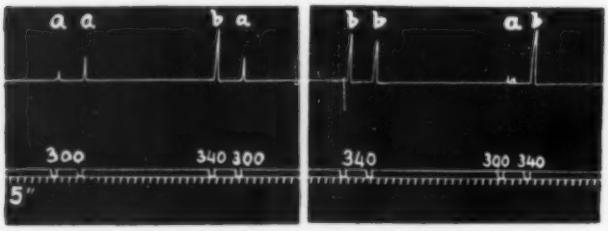


FIG. 21. Feb. 14, 1935. *Macaca mulatta*. Dial-narcosis. This figure shows the effect of change in voltage alone. "a" facilitates "a" and "b"; "b" facilitates "a", but extinguishes "b".

d. *Pairs unequal in voltage only*. Figure 21 presents an experiment in which only the voltage is altered. The stimulation of lower voltage always facilitates, that of higher voltage, while it facilitates the response to stimulation of lower voltage, extinguishes the response to itself. This finding is in entire harmony with that presented in Fig. 16, in which stimulation at the higher voltage, which failed to produce facilitation as judged by increase of amplitude of response to itself, brought in a response to voltages previously subliminal.

That in the pair "ba" the response to "a" is facilitated is clear by comparing this response with the first and seventh responses, which are unaffected by antecedent stimulation.

In experiments wherein the voltage of stimulation is changed there is inherent a complexity not encountered in experiments with other inequalities of stimulation at a single focus. For not only is there with increase of voltage an increase in the percentage of nerve cells stimulated in the area reached by stimulation with lower voltage, but also an increase of the area affected (greater spread of current). To which of these an observed change of response is to be referred is, of course, uncertain, which precludes further analysis.

The changes in the population of nerve cells directly excited when voltage or pulse-form is changed, is a complexity absent when only pattern-frequency or duration is changed. Since with changes of one of the latter

parameters alone the same population of nerve cells is excited—either more frequently by higher pattern-frequency or more often by longer duration—changes of threshold become of paramount importance and the results referable to the factors for facilitation and extinction.

4. *Triple stimulation*

At this point the findings with triple stimulation (see Fig. 3) must be considered in conjunction with parallel experiments on electrical activity and slow voltage drifts. The significant finding in such parallel experiments is that whereas the first stimulation initiates electrical afterdischarge and negative voltage drift followed by positive voltage drift, the second stimulation elicits no electrical afterdischarge but does produce a negative voltage drift which is consistently associated with decreased latency of the third (facilitated) response, irrespective of the amplitude of this response. This confirms one in the opinion that facilitation as expressed by decrease of latency of response is associated with decrease in threshold to repetitive stimulation, rather than with involvement of new neurones, excited transsynaptically by afterdischarge, which by summation is unquestionably a factor for increase of amplitude.

E. *Predictions*

1. *Conditions for reversal of a cortical focus*

All the facts and considerations enumerated above led to certain predictions concerning the apparent reversal of a cortical focus by antecedent stimulation of a related antagonistic focus. The predictions were that, irrespective of whether the stimulation of the focus to be reversed was predominantly facilitating or extinguishing at the interval under investigation, the reversal would occur provided 1. that the antecedent stimulation of the antagonistic focus produced strong primary facilitation at the interval in question; 2. that the primary facilitation of this antagonistic focus be such as to exhibit increase of amplitude or afterdischarge and not merely decrease of latency.

This reversal of a cortical focus was designated above as an apparent reversal because the evidence presented led to the conclusion that the reversal does not depend upon any change at the focus reversed nor even upon a fall in threshold of the antagonistic focus, but upon persistence of activity involving lower levels of the CNS, *e.g.* the spinal cord. A reversal of response in which the cortex certainly plays a significant rôle has been observed with relatively prolonged stimulation of a single focus so as to extinguish it and facilitate a neighbouring antagonistic focus. These predictions have been verified by the following results, all of which can be seen in one figure, namely Fig. 22. This figure presents six records, each consisting of four pairs of stimulations to two cortical foci, 3 mm. apart, one for extension (E) and one for flexion (F) at the elbow.

The antagonistic movements of the forearm at this joint were recorded with two tambours, the levers of which were attached with threads to the forearm just above the wrist. In the resting position these threads were just slack with the intention of obtaining independent records of the two mo-

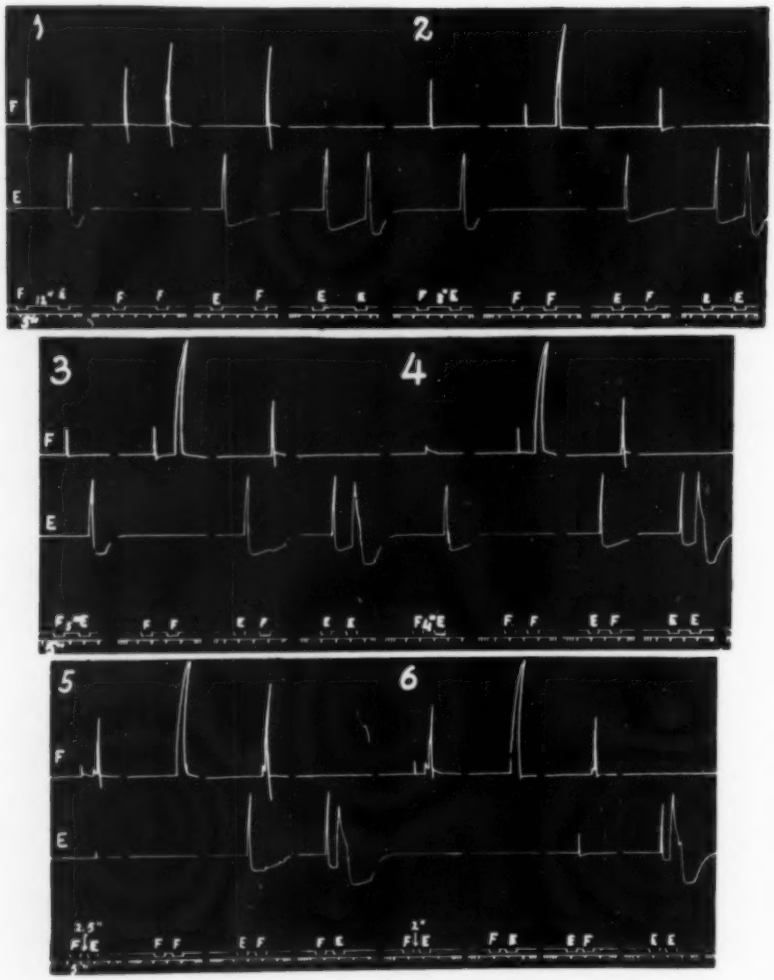


FIG. 22. Jan. 26, 1937. *Macaca mulatta*. Dial-narcosis. This figure shows records of flexion and extension at elbow upon cortical stimulation of a flexor and an extensor focus respectively. In record 5 the appearance of a flexor response to E stimulation will be seen; for complete reversal see first graph of record 6. For further details see text. All parameters of stimulation constant throughout; only interval gradually shortened.

tions. The excursions of the levers were recorded on the kymograph by means of two tambours, the upper recording the flexion, the lower the extension at the elbow. All stimulations were kept constant throughout the

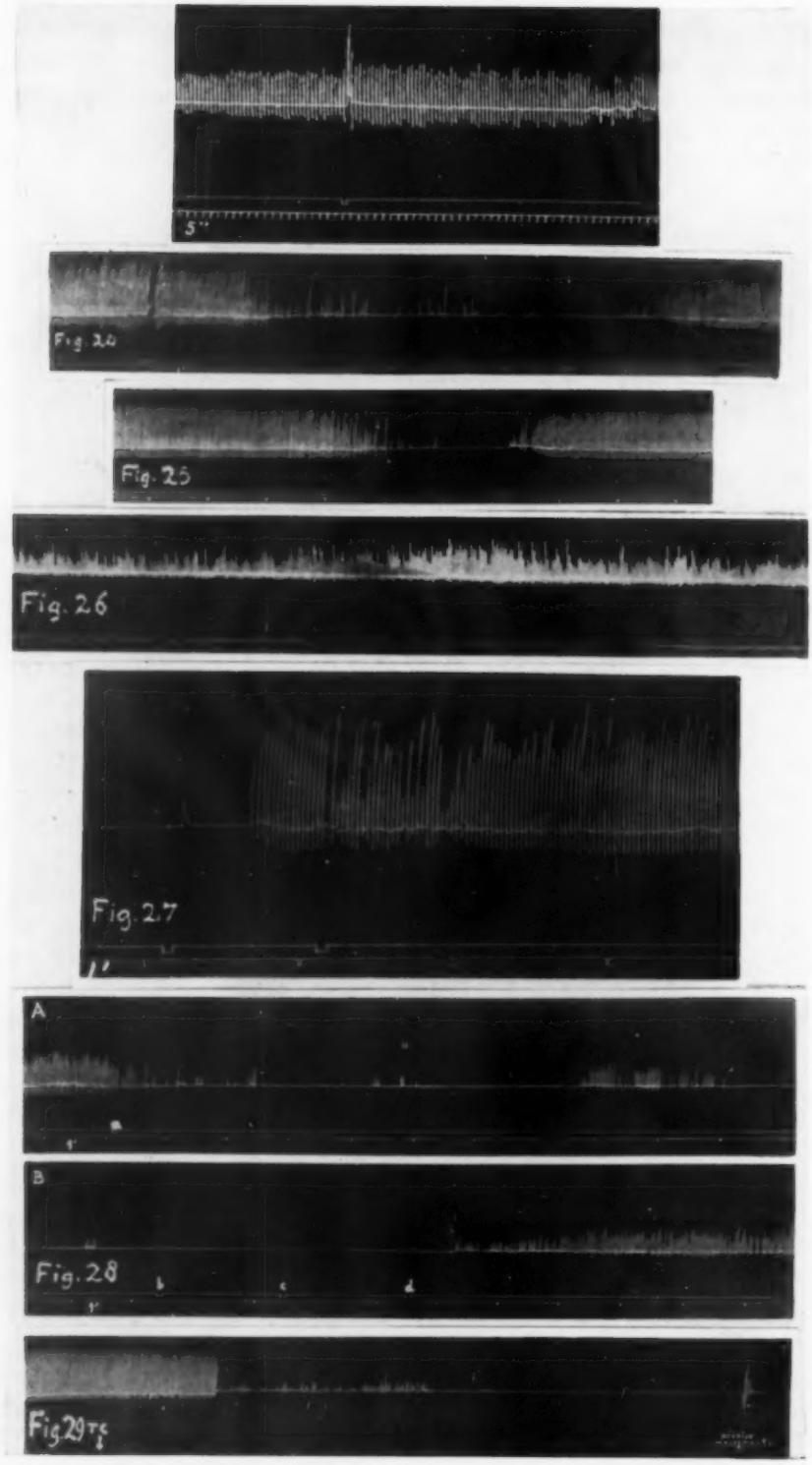
experiment and only the interval was decreased from record to record. The parameters of stimulation were chosen to produce primary facilitation at all intervals at the F focus, extinction with long and facilitation with very short intervals at the E focus.

Complete reversal can be seen in the first pair of responses (FE) of record 6, where stimulation of E 2 sec. after stimulation of F results in flexion only. This reversal is not obtained with antecedent extinguishing stimulation of the antagonistic focus (see pairs EF and EE of record 1), nor with weakly facilitating stimulation (see pairs FE and FF of records 1, 2, 3 and 4), but only with strongly facilitating stimulation (pairs FE and FF of records 5 and 6). Nor is facilitation as judged by decrease in latency alone sufficient to produce reversal (pairs EF and EE of records 2 through 6) even when, as in record 6, the latency is reduced to a minimum.

Thus, these findings fulfil the predictions that in order to obtain the apparent reversal of a cortical focus the stimulation of the antagonistic focus must be such as to produce primary facilitation, *i.e.* increased responsiveness to repetition of stimulation at that same focus, as judged by increase of amplitude (usually accompanied by motor afterdischarge) at the interval in question.

Scrutiny of these records brings out another interesting relation of the E and F responses. Reversal of a cortical focus necessarily includes diminution of the normal response to stimulation of the "reversed" focus, as shown by the gradual decline of the E responses in pairs FE in all records of Fig. 22 (as well as the appearance of the F response to the E stimulation). This diminution cannot be considered as an extinction of this response, but must be interpreted as an *inhibition* in the extensor systems due to activity in the reciprocally related flexor systems, which finally in records 5 and 6 produce the F response to E stimulation. But that is not all. The E stimulation is predominantly extinguishing reaching its maximal effectiveness at an interval of 2.5 sec. The underlying decrease in activity of the extensor systems (extinction) should then manifest itself as an increased response to the F stimulation. That such is the case is seen in the increase in the F responses in the EF pairs of records 1 through 5. The decrease of this same response in record 6 at an interval of 2 sec. is caused by the appearance of some facilitation in the extensor systems at this short interval, seen in EE of this record.

One more point in regard to Fig. 22 should be noted. The stimulation to the F focus being facilitating, and the E stimulation not, there is always more excitation in the flexor than in the extensor systems. With decrease in interval and the eventual appearance of flexor response to the E stimulation this increased activity of the flexor system results in extinction in that system, as evidenced by the gradual decline, from record to record, in the size of the first response in each FF pair and their eventual disappearance in records 5 and 6. It is well to take this point into consideration in judging the amount of facilitation in these pairs in the successive records of Fig. 22.



FIGS. 23–29. (*For legends see opposite page.*)

2. *Changes in the knee-jerk*

Consideration of the above findings with the observations of long lasting changes in activity induced in the spinal cord by cortical stimulation (see sub C.1.d.), led to several predictions as to the effect of cortical stimulation on "spinal" reflexes. To test these predictions the knee-jerk (KJ) was elicited periodically[19] and changes in its amplitude induced by cortical stimulation recorded kymographically. The predictions were the following: 1. facilitating stimulation of a cortical focus for extension at the knee will produce a long lasting facilitation of the KJ; 2. extinguishing stimulation of the same focus will produce a prolonged diminution (extinction) of the KJ; 3. facilitating stimulation of an antagonistic cortical focus, yielding flexion at the knee, will result in a prolonged diminution (inhibition) of the KJ; 4. extinguishing stimulation of this same focus will enhance the KJ.

Inasmuch as this enhancement is due to factors for extinction in antagonistic systems we would avoid the term facilitation.

As corollaries to the foregoing it can be predicted that facilitating stimulation of an extensor focus and extinguishing stimulation of a flexor focus should bring back the KJ when it has been obliterated either by extinguishing stimulation of an extensor focus or facilitating stimulation of a flexor focus, and finally that passive movements at the knee will bring back by facilitation an extinguished or inhibited KJ.

Figure 23 shows the temporary *facilitation* of the KJ following facilitating stimulation of a focus for extension at the knee. Figure 24 shows the temporary *extinction* of the KJ following extinguishing stimulation of a focus for extension at the knee. Figure 25 shows the temporary *inhibition* of the KJ following facilitating stimulation of a focus for flexion at the knee.

FIG. 23. Feb. 18, 1937. *Macaca mulatta*. Dial-narcosis. *Facilitation* of knee-jerk by *facilitating* stimulation (0.3μF, 40/″, 3 sec., VD = 5500) of a focus of L.4 for *extension* at the knee.

FIG. 24. Nov. 17, 1938. *Macaca mulatta*. Dial-narcosis. *Extinction* of knee-jerk by *extinguishing* stimulation (0.6μF, 80/″, 6 sec., VD = 1000) of a L.4 focus for *extension* at the knee.

FIG. 25. Nov. 17, 1938. Same animal as of Fig. 22. *Inhibition* of knee-jerk by *facilitating* stimulation (0.3μF, 30/″, 4 sec., VD = 9000) of a L.4 focus for *flexion* at the knee.

FIG. 26. Nov. 8, 1938. *Macaca mulatta*. Dial-narcosis. KJ elicited every 2 sec. *Enhancement* of KJ by *extinguishing* stimulation (1μF, 80/″, 6 sec., VD = 500) of an L.4 focus for *flexion* at the knee.

FIG. 27. Nov. 17, 1938. *Macaca mulatta*. Dial-narcosis. KJ *extinguished* by *extinction* of an L.4 focus for *extension* at knee. KJ *returns* after *facilitating* stimulation of *same* focus.

FIG. 28. Nov. 17, 1938. Same animal as of Fig. 25. In record A *inhibition* of KJ after *facilitating* stimulation (0.3μF, 30/″, 4 sec., VD = 7000) of a L.4 focus for *flexion* at knee. In record B *return* of KJ after repeated *facilitating* stimulation (1μF, 80/″, 6 sec., VD = 1000) of *same* focus.

FIG. 29. Nov. 21, 1938. *Macaca mulatta*. Dial-narcosis. Disappearance of KJ after *thermocoagulation* at 80°C for 5 seconds of the area (3 mm.^{2})of L.4 from which *extension* at knee could be elicited. The KJ was absent for 15 hours and could then be brought back only by often repeated passive movements of leg at knee and even then its amplitude was small and irregular.

Figure 26 shows the temporary *enhancement** of the KJ following extinguishing stimulation of a focus for flexion at the knee. Figure 27 shows the return of the KJ by repeated facilitating stimulation of that focus for extension at the knee, extinguishing stimulation of which had extinguished the KJ. Figure 28 shows the return of the KJ by repeated extinguishing stimulation of that focus for flexion at the knee, facilitating stimulation of which had inhibited the KJ.

Each of the above predictions has, therefore, been verified. These findings in the KJ beautifully illustrate the importance of a proper balance of these reciprocally related flexor and extensor systems in the maintenance of the normal KJ. Obviously to these systems belong those flexor and extensor foci in the cortex, the stimulation of which, as shown above, profoundly changes the KJ. It became of interest, therefore, to investigate whether the destruction of one of these antagonistically, or reciprocally, related foci, leaving the other intact, would not so upset the balance of these systems as to alter the KJ demonstrably.

To answer this question the cortical area for extension at the knee of a monkey was mapped and found to be *ca.* 2 mm. in diameter. Extinguishing stimulation of the center of this area resulted in typical extinction of the KJ, which was reinitiated by passive flexions and extensions at the knee. After the KJ had returned to normal this extensor area was precisely thermocoagulated (80°C for 6 sec.), which after 2 min. resulted in an abrupt and almost complete obliteration of the KJ which became complete at the end of 4 min. Attempts to reinitiate it by passive movements at the knee resulted only in a few rapidly declining KJs (see Fig. 29). Extinguishing stimulation of the adjacent intact cortical flexor focus although resulting in prompt flexor responses at the knee failed to bring back the obliterated KJ. Fifteen hours after this thermocoagulation the KJ was still absent and when restored, after many attempts at facilitation by passive movements at the knee, was small and irregular. This experiment shows that in the monkey, even under narcosis, cortical impulses impinge upon the spinal cord and that cessation of impulses arising in a cortical focus for extension at the knee is sufficient to produce an imbalance between the extensor and flexor systems thus obliterating the KJ.

That it is a specific imbalance between the extensor and flexor systems rather than the elimination of non-specific cortico-spinal impulses, maintaining the general level of activity in the spinal cord, follows from the observation that thermocoagulation of the whole precentral leg area (L.4, L.4-S and L.6) results only in a very transient diminution of the KJ for *circa* 5 minutes, after which it returns to its original amplitude. The finding that a very circumscribed cortical lesion results in the loss of a reflex usually considered spinal and that an extensive destructive lesion of the cortex, including this area, does not result in this disorder is obviously of interest in regard to the problem of functional localization in the cortex.

* For the choice of this designation see p. 347.

Discussion

Before entering into the discussion it seems advisable to sum up the main points of the results presented. The first point is that it is now established that underlying facilitation and extinction are changes in the CNS induced by antecedent activity, not by mere passage of current. Second, that these changes differ in kind, in time and in space. Third, that they can operate only by affecting threshold and (or) activity and that in the living CNS a change in either of these inevitably induces a change in the other.

We have isolated for study the electrical activity, the slow potentials and the pH and examined these at the site of stimulation and at remote parts of the CNS, and correlated them with facilitation and extinction. This analysis has shown that increased activity, increased excitability associated with negative voltage drift and a probable alkalinity are factors for facilitation, that decreased activity, decreased excitability associated with positive voltage drift and acidity are factors for extinction. On the basis of these findings it was possible to explain some of the findings with pairs of unequal stimulations and to predict and verify conditions for "reversal" of a cortical focus and for changes in the knee-jerk induced by cortical stimulation.

The following points need more detailed consideration: (i) as stated in a previous paper (13, p. 523) it was Lorente de Nó who suggested that the diminution or absence of response to test stimulation might result from an absence of background-activity in reverberating circuits, because they have been forced to discharge simultaneously and, therefore, have become simultaneously refractory. The first part of this suggestion has been more than substantiated; for the rapid phase of an electrical afterdischarge is always associated with facilitation, the diminution or absence of electrical activity following hyperactivity, whether due to direct stimulation or to an afterdischarge propagated transsynaptically to the area under investigation, is always associated with extinction. Our technique has not been such as to allow verification of the second part of Lorente de Nó's suggestion, except for this, that stimulation during the latter part of a prolonged electrical afterdischarge regularly terminates it.

In this connection it is of interest to examine the typical form of an electrical afterdischarge as exemplified in Fig. 10 in the record from area L.3. Following the long period during which this area has received impulses from the area stimulated (L.4) the active discharge of the area itself is characterized by a burst of rapid electrical fluctuations of remarkably constant form and interval; these end abruptly and are followed by much larger fluctuations of an entirely different form and lower frequency. This type of change may be repeated several times during a single afterdischarge until the frequency has dropped to about 3 per sec. The end of the discharge may exhibit a gradual decline in voltage (as in Fig. 10), but often ends abruptly, in either case followed by diminution of electrical activity. This sudden drop in frequency associated with a change in wave form is what one would expect from Lorente de Nó's work[32–35] for short chains being discharged

more frequently than long chains will sooner suffer a rise in threshold and cease to conduct, leaving only the longer circuits active.

This interpretation receives support from experiments on electrical afterdischarge in monkeys before and after deep undercutting of the cortex. For, following such a lesion the picture of afterdischarge is unchanged except for the absence of the slower, about 3 per sec. rhythms. This indicates that the circuits for the higher frequencies of afterdischarge are purely cortical or cortico-cortical, whereas those for the low frequencies are relayed back to the cortex by subcortical or even lower structures.

This analysis explains why one finds extinction, not facilitation, during the slow, terminal phase of an afterdischarge, for at this time too many cells have become inexcitable. As one would expect from this and as stated on p. 331 this latter part of an electrical afterdischarge is associated with a positive voltage drift.

(ii). This brings us to the slow voltage changes that follow prolonged enforced activity. We not not wish to call these phenomena after-potentials; first, because, strictly speaking, they are not potentials in the sense of the physicist, and second, because the conditions for experimentation are not those for which an after-potential is defined, namely as alteration in the voltage of a current of injury (*positive Nachschwankung* of Ewald Hering[23]) in excised nerve. Nor do we wish to use Gasser's designation[22] for somewhat similar phenomena in the spinal cord, which he calls intermediary potentials, not only because this again introduces the notion of potentials, but also because it refers the phenomena at hand to particular structures, namely internuncial neurones.

We are indebted to Dr. C. H. Prescott of the Bell Telephone Laboratories for calling to our attention that an electrical potential is not defined in the presence of a chemical reaction or where for any other reason there is a change in the carrier of the current, *i.e.* from an ion in solution to an electron in a wire or *vice versa*. What one observes under these conditions, *i.e. in all ordinary electrophysiological experiments*, are, strictly speaking, voltages, not potentials. For these reasons the designation "voltage drifts" seems to us the simplest, appropriate and noncommittal description. The term "drift" seems the more appropriate because these slow changes in voltage are presumably not the cause for the changes in threshold but merely one expression of those processes which underlie the accompanying changes in threshold.

Though these voltage drifts resemble in many points those observed in peripheral nerve and the spinal cord,[22] they are usually much larger and more prolonged. The negative drift in Fig. 13[2] for instance lasted about 20 sec., the ensuing positive drift between 5 and 10 minutes! Points of resemblance are: *a.* the sequence, *i.e.* negativity followed by positivity; *b.* the susceptibility to various conditions, such as temperature, poor local blood supply or poor general circulation, partial asphyxia. In our experiments on the cortex the depth of Dial-narcosis has been shown (Fig. 13) to be also of

great importance, though we are not in a position to exclude entirely some element of lesser ventilation, since the animal breathed spontaneously. Finally these voltage drifts are augmented with increase of the number of neurones discharged and with the number of times they are discharged. This resemblance is not surprising if one considers the great number of nerve fibers in the cortex.

But irrespective of whether the processes underlying these voltage drifts are the same in cortex, cord and nerve, their association with the change in threshold to repetitive stimulation is always the same; negativity is associated with increased responsiveness, positivity with decreased responsiveness. It is of interest to point out that while the manner of picking up these voltage drifts on the cortex (without injury) is entirely different from that of picking up the after-potentials in an excised peripheral nerve (from longitudinal and cut surface), both are explicable in terms of the membrane-theory, for in both negativity is associated with a decrease and positivity with an increase of the "membrane-potential" in cells or fibers that have been discharged; the essential condition being that one electrode is at the site of this discharge, the other at an unaffected site, be it a remote focus in the cortex or the killed end of a peripheral nerve.

We have so far discussed the neural activity evidence by electrical activity at the time and place in question and the slow voltage drifts indicative of threshold changes then and there. Both of these changes are concerned only with neurones already involved. It was because it was impossible to frame a plausible explanation for the facilitation encountered in the experiments with unequal pairs of stimulations, and because of the persistence of diminished electrical activity and extinction beyond the period of positive voltage drift that we were forced to seek for a third variable, which would affect the threshold not only of neurones that had been discharged, but also the threshold of any neurones in their vicinity, whether previously excited or not. It was obvious that this variable must involve changes in the "milieu" of the neurones in question and was, therefore, presumably a change in ionic constitution. Obviously an investigation of the pH of the cortex was in order and, when made, the pH was found to be significant.

(iii). The specificity of the axonal terminals of the myriads of nerve cells in a given area of the cortex is so great that the consequences of a change in pH of a given area, carrying with it the alteration of activity of cells not involved in the response to a given stimulus, cannot be seen as yet in detail. Antagonistic cortical foci lie often so close together as to be affected contemporaneously by a local pH change. For this reason it is difficult to see how changes in pH could be responsible for the rapid contrasting phenomena encountered in reciprocal innervation, which imply changes of opposite sign in neighbouring neurones. On the other hand the changes in threshold of a cell or cell-group associated with a slow voltage drift are discrete and limited to the cells discharged. In fact it is in terms of threshold changes of particular cells in the spinal cord that Gasser[21] has offered an explanation of re-

ciprocal inhibition. Thus it is possible to account for the inhibition encountered in reciprocal innervation in terms of a factor for extinction; it is obviously impossible to account for extinction in terms of inhibition, since extinction is a change in the system due to antecedent activity in that same system and, therefore, does not require a relation with an antagonistic system.

(iv). In conclusion we wish to mention briefly one more point. It is of interest to note that whereas the motor responses to constant intermittent electrical stimulation of a "motor" focus show typical "waves,"[6,24] the spontaneous electrical activity of the cortex, without stimulation, does not show corresponding fluctuations. One is, therefore, driven to regard the occurrence of these waves as a consequence of the stimulation itself, *i.e.* as

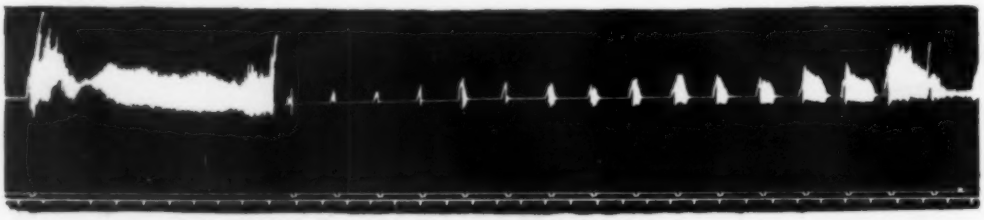


FIG. 30. Feb. 26, 1936. *Macaca mulatta*. Dial-narcosis. Continuous subthreshold background stimulation at 5 per second of a "motor" focus for extension of wrist and intermittent repetitive stimulation (96 per sec.) at periods indicated by upper signal marker. Time = 20 sec. The important thing to note is that the motor activity shown is *not* a motor afterdischarge following the intermittent stimulations, but responses to the background stimulation facilitated by the intermittent stimulations. The second indicates rapid and slow changes in the responsiveness of the nervous systems involved. At the end of the record a new slow cycle begins; the whole record represents, therefore, a little more than one whole slow cycle of the order of 10 minutes' duration.

being due to factors for facilitation and extinction. It is possible to verify this conclusion with the following experiment (see Fig. 30). One "motor" focus is stimulated from two independent sources, one of which delivers a background stimulation of 5 pulses per sec., which by themselves are just subthreshold. The other source delivers once every 34 sec. for a period of 3 sec., stimulation at 96 short pulses per sec. which when applied for the first time, and superimposed upon the background stimulation, results for 190 sec. in a series of responses to the latter stimulation. In Fig. 30 it will be seen that the first responses of this series are very large, then gradually diminish, then return to an intermediate size to end abruptly with a few large responses. During this period of responses to background stimulation the intermittent stimulation was omitted, so as not to interfere with the facilitated motor responses to the background stimulation. After the cessation of these responses the intermittent stimulation was reinstated and it will be seen 1. that each of these stimulations results in a temporary reappearance of motor responses to the background stimulation, 2. that these gradually become larger and more persistent. At the end of the record an entire cycle

begins again. After all the foregoing the interpretation is not difficult. The first of the intermittent stimulations facilitates the response to the background stimulation in two ways: (i). by the relatively local changes of threshold and, (ii). by the more widely spread afterdischarge. The first of these runs a short course leading to extinction, producing a minimum of response at 40 sec. (positive drift at the site of stimulation), whereas the second runs a much longer course (typical of electrical afterdischarge in cortex and cord) to end abruptly in extinction (extinction due to involvement of remote cortical foci and spinal structures). The dissipation of this extinction is clearly exhibited in the latter two-thirds of the record. It is important to note that the prolonged facilitation which parallels an electrical afterdischarge cannot be repeated for many minutes, whereas the short-lived facilitation associated with negative voltage drift is repeatable within about half a minute after the end of the facilitated responses associated with electrical afterdischarge. This again confirms the finding mentioned sub D.4 (p. 343).

Figure 30 shows that regular intermittent repetitive stimulation of the cortex sets up slow rhythmical changes in its responsiveness and indicates that underlying the "waves" of cortical excitability are the more persistent factors for facilitation and extinction in parts of the CNS distant from the site of stimulation. These are, for facilitation, the electrical afterdischarge and its associated slow negative voltage drift (and probably alkalinity) and, for extinction, the diminution of electrical activity, its associated slow positive voltage drift and certainly acidity.

Conclusions

Facilitation and extinction are alterations induced in the response to test stimulation by antecedent stimulation. Underlying facilitation and extinction are changes in the activity and threshold of the parts of the CNS involved in the response to test stimulation. These changes, initiated by antecedent excitation, differ in kind and vary in intensity from time to time and from place to place.

For *facilitation* the factors are: (i). hyperactivity yielding increased summation; (ii). negative voltage drift associated with decrease of threshold in neurones previously involved; (iii). probably increase of pH (alkaline shift) decreasing the threshold of all neural structures in the region involved. For *extinction* the factors are: (i). hypoactivity resulting in less summation; (ii). positive voltage drift associated with increase of threshold in neurones previously involved; (iii). decrease of pH (acid shift), increasing the threshold of all neural structures in the region involved.

The effects of choice of the parameters of antecedent and test stimulation and of the interval between them upon latency, threshold and amplitude of response are explicable in terms of the modes of action of these factors.

The findings presented in this paper offer an approach to the problem of reciprocal innervation, for they compel now verified prediction of (i). the

conditions for apparent reversal of a cortical focus, and (ii). the changes in the knee-jerk following facilitating or extinguishing stimulation of a cortical focus for extension or flexion at the knee. Inhibition in reciprocal innervation is explicable in terms of the more discrete factors for extinction.

The "waves" of cortical excitability, previously described, are referable to the more remote and prolonged factors for facilitation and extinction.

REFERENCES

1. Adrian, E. D. The spread of activity in the cerebral cortex. *J. Physiol.*, 1936, *88:* 127–161.
2. Bartley, S. H., and Bishop, G. H. The cortical response to stimulation of the optic nerve in the rabbit. *Amer. J. Physiol.*, 1933, *103:* 159–172.
3. Bishop, G. H. Cyclic changes in excitability of the optic pathway of the rabbit. *Amer. J. Physiol.*, 1933, *103:* 213–224.
4. Bishop, G. H. La théorie des circuits locaux permet-elle de prévoir la forme du potentiel d'action? *Arch. int. Physiol.*, 1937, *45:* 273–297.
5. Bishop, G. H., and O'Leary, J. Components of the electrical response of the optic cortex of the rabbit. *Amer. J. Physiol.*, 1936, *117:* 292–308.
6. Brody, B. S., and Dusser de Barenne, J. G. Effect of hyperventilation on the excitability of the motor cortex in cats. *Arch. Neurol. Psychiat., Chicago*, 1932, *28:* 571–585.
7. Bubnoff, N., and Heidenhain, R. Ueber Erregungs- und Hemmungsvorgänge innerhalb der motorischen Hirncentren. *Pflüg. Arch. ges. Physiol.*, 1881, *26:* 137–200.
8. Burr, H. S., Lane, C. T., and Nims, L. F. A vacuum tube microvoltmeter for the measurement of bioelectric phenomena. *Yale J. Biol. Med.*, 1936, *9:* 65–76.
9. Dusser de Barenne, J. G. Simultaneous facilitation and extinction of motor response to stimulation of a single cortical focus. *Amer. J. Physiol.*, 1936, *116:* 39–40.
10. Dusser de Barenne, J. G. Simultane Bahnung und Auslöschung in der "motorischen" Hirnrinde. *Conf. neurol.*, 1938, *1:* 1–4.
11. Dusser de Barenne, J. G., and McCulloch, W. S. An "extinction" phenomenon on stimulation of the cerebral cortex. *Proc. Soc. exp., Biol. N. Y.*, 1934, *32:* 524–527.
12. Dusser de Barenne, J. G., and McCulloch, W. S. Extinction: local stimulatory inactivation within the motor cortex. *Amer. J. Physiol.*, 1935, *113:* 97.
13. Dusser de Barenne, J. G., and McCulloch, W. S. Local stimulatory inactivation within the cerebral cortex, the factor for extinction. *Amer. J. Physiol.*, 1937, *118:* 510–524.
14. Dusser de Barenne, J. G., and McCulloch, W. S. Functional organization in the sensory cortex of the monkey (*Macaca mulatta*). *J. Neurophysiol.*, 1938, *1:* 70–85.
15. Dusser de Barenne, J. G., and McCulloch, W. S. Kritisches und Experimentelles zur Deutung der Potentialschwankungen des Elektrocorticogramms. *Z. ges. Neurol. Psychiat.*, 1938, *162:* 815–824.
16. Dusser de Barenne, J. G., McCulloch, W. S., and Nims, L. F. Changes of hydrogen ion concentration of the cerebral cortex. *Proc. Soc. exp. Biol., N.Y.*, 1937, *36:* 462–464.
17. Dusser de Barenne, J. G., McCulloch, W. S., and Nims, L. F. Functional activity and pH of the cerebral cortex. *J. cell. comp. Physiol.*, 1937, *10:* 277–289.
18. Dusser de Barenne, J. G., Marshall, C. S., McCulloch, W. S., and Nims, L. F. Observations of the pH of the arterial blood, the pH and the electrical activity of the cerebral cortex. *Amer. J. Physiol.*, 1938, *124:* 631–636.
19. Dusser de Barenne, J. G., and Ward, A. A., Jr. Reflex inhibition of the knee-jerk from intestinal organs. *Amer. J. Physiol.*, 1937, *120:* 340–344.
20. Gasser, H. S. Changes in nerve-potentials produced by rapidly repeated stimuli and their relation to the responsiveness of nerve to stimulation. *Amer. J. Physiol.*, 1935, *111:* 35–50.
21. Gasser, H. S. The control of excitation in the nervous system. *Harv. Lect.*, 1937, *32:* 169–193.
22. Gasser, H. S., and Graham, H. T. Potentials produced in the spinal cord by stimulation of dorsal roots. *Amer. J. Physiol.*, 1933, *103:* 303–320.

23. HERING, E. Beiträge zur allgemeinen Nerven- und Muskel-physiologie. XV. Mittheilung. Über positive Nachschwankung des Nervenstromes nach elektrischer Reizung. *S.B. Akad. Wiss. Wien.*, 1884, *87:* 137–158.
24. HOVLAND, C. I., and DUSSER DE BARENNE, J. G. Periodic fluctuations in motor response to uniform electrical stimulation of the cerebral cortex in monkeys. *Amer. J. Physiol.*, 1936, *116:* 79.
25. LANE, C. T., MCCULLOCH, W. S., PRESCOTT, C. H., and DUSSER DE BARENNE, J. G. A new method for the investigation of the electrical proprties of living tissues. *Amer. J. Physiol.*, 1935, *113:* 85.
26. MARSHALL, W. H., WOOLSEY, C. N., and BARD, P. Cortical representation of tactile sensibility as indicated by cortical potentials. *Science*, 1937, *85:* 388–390.
27. MARSHALL, W. H., WOOLSEY, C. N., and BARD, P. in MACLEOD, *Physiology in modern medicine*, 8th ed. St. Louis, C. V. Mosby and Co., 1938 (see 168–173, 194).
28. MCCULLOCH, W. S. On the nature and distribution of factors for facilitation and extinction in the central nervous system. *Amer. J. Physiol.*, 1937, *119:* 363–364.
29. MCCULLOCH, W. S., and DUSSER DE BARENNE, J. G. Action potentials of the cerebral cortex and spinal cord before and after cortical stimulation. *Amer. J. Physiol.*, 1936, *116:* 99.
30. MCCULLOCH, W. S., and DUSSER DE BARENNE, J. G. The knee-jerk following facilitating or extinguishing stimulation of related cortical foci. *Amer. J. Physiol.*, 1939 (in press).
31. MCCULLOCH, W. S., and WENDT, G. R. Photokymographic method with continuous cathode ray oscillograms. *Science*, 1936, *83:* 354–355.
32. LORENTE DE NÓ, R. The synaptic delay of the motoneurones. *Amer. J. Physiol.*, 1935. *111:* 272–282.
33. LORENTE DE NÓ, R. The refractory period of the motoneurones. *Amer. J. Physiol.*, 1935, *111:* 283–288.
34. LORENTE DE NÓ, R. Facilitation of motoneurones. *Amer. J. Physiol.*, 1935, *113:* 505–523.
35. LORENTE DE NÓ, R. Analysis of the activity of the chains of internuncial neurons. *J. Neurophysiol.*, 1938, *1:* 207–244.
36. SCHMITT, O. H. A., and SCHMITT, F. O. A universal precision stimulator. *Science*, 1932, *76:* 328–330.

CONTROL BY THE CENTRAL NERVOUS SYSTEM OF RECTAL SMOOTH MUSCLE

ORTHELLO R. LANGWORTHY AND SEYMOUR J. ROSENBERG
Sub-department of Neurology, the Johns Hopkins University, Baltimore, and Veterans' Administration Hospital, Perry Point, Maryland

(Received for publication April 1, 1939)

WE HAVE developed the theory that smooth muscle is controlled by reflex arcs involving nearly all portions of the central nervous system. Experimental and clinical observations have demonstrated its applicability to the muscle of the urinary bladder (Langworthy, Lewis, Dees and Hesser, 1936). The muscular wall of the different viscera is adapted to particular functional demands; this must influence the manner of its control by the brain and cord. The smooth muscle of the rectum has been chosen for extending this investigation, because it again is accessible for experimental work in mammals and man.

Stimulation of the cerebral motor cortex under favorable conditions modifies peristalsis in the gastro-intestinal tract (Watts, 1935; recent work has been summarized by Fulton, 1938, p. 479). Removal of the premotor cortex may produce violent peristalsis, giving rise to intussusception in monkeys. Patients with damage to the ventral surface of the brain stem are prone to develop hemorrhages and ulcers in the mucosa of the stomach and intestines. The observation that many epileptics have gastro-intestinal aurae has been correlated with the cerebral representation of these areas. Denny-Brown and Robertson (1935) have studied the relation of activity in the rectum to that of the anal sphincters, and the control of this mechanism both by the peripheral nervous plexus and by the spinal cord. Records were made on normal man, patients with cauda equina lesions and others with transection of the spinal cord. Contraction of the rectal musculature always led to relaxation of the internal and external anal sphincters. Since this relation exists, we have examined only the activity of the muscle of the rectal wall and disregarded the sphincters. Our observations have included experiments on 12 cats before and after removal of portions of the central nervous system, and records of activity of the rectal muscle in patients with hemiplegia and paraplegia. The experimental results are given here.

Our records were obtained by means of the apparatus shown in Fig. 1. A rubber balloon, approximately two inches long, which held 20 cc. of air before stretching began, was connected by means of thick walled rubber tubing to a U-shaped water manometer of 3 mm. bore. The distal end of the manometer was in turn attached to a tambour which recorded on a kymograph the transmitted changes of pressure within the balloon. The lubricated, uninflated balloon was inserted into the cat's rectum well above the sphincters. By means of a luer syringe 5 cc. increments of air were injected into the balloon through a T-tube. Air was prevented from escaping from the system by the use of a two-way valve. The height of the distal column of water was noted immediately before and after the instillation of air. The difference in height of this column of water was an indication of the relative changes of pressure occurring within the balloon. Although the pressure readings are not absolute values, the fact that we used the same manometer in all experiments renders the pressure changes directly comparable. Respiratory excursions were recorded by means of an inflated balloon fastened to the animal's chest and connected to a tambour.

Time was marked at 5 sec. intervals. Under deep ether narcosis, a tracheal tube was inserted and the cat's lungs were inflated periodically by means of a Harvard respirator. A normal reading of rectal responses to progressive distention was made. The carotid arteries were then tied, and the cat was decerebrated at the level of the superior colliculus. After the bleeding was well controlled, another study of the rectal muscle was made. In like manner readings were obtained following transections between the optic and acoustic colliculi, below the vestibular nuclei, in the lower medulla, and spinal cord.

To determine the pressure changes due to the elastic properties of the balloon itself,

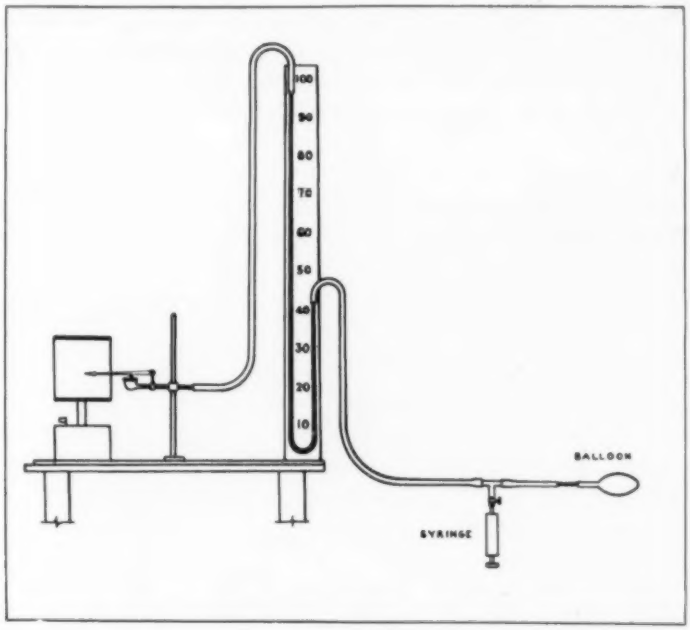


FIG. 1

a graph was made by adding 5 cc. increments of air to the balloon outside of the animal (Fig. 2A). At low volumes there is an increasing resistance of the balloon to stretch, observed as greater changes in pressure for each increment of volume. At greater volumes the resistance of the rubber to stretch diminishes until a point is reached where it is so negligible that no further changes in pressure appear to occur. In our animal experiments no more than 11 increments of air were added to the balloon, so that only the first third of graph 2A need be used for comparison. Readings were made in several animals 5 min. after death (Fig. 2B). It is known that smooth muscle lives for several hours after the death of an animal. At the beginning of filling no marked increase of pressure was obtained on adding increments of air. This is due in part to the fact that the balloon was not sufficiently inflated to produce stretch of the rectal wall. Later the increments of pressure increased progressively as the constant volumes were added. The record is similar to the first portion of distention in graph A. Toward the end of filling rhythmic waves of rectal contractions were seen. These show that the rectal muscle was still capable of contracting. In these two graphs the endeavor was made to demonstrate resistance to distention of the rubber balloon alone and then of both the balloon and the relatively inert rectal wall. These two are measured simultaneously in the experiments. In the live animal a third important factor must be considered, the added influence of the nervous system. It was impossible to procure an ideal type of preparation in which to show the findings illustrated in graph B. Theoretically we should have waited for many hours until the smooth muscle was quite dead. But then rigor mortis would have been a complicating factor. On the other hand if the record had been made from a live cat with all the nerve trunks to the rectal wall cut, we would have measured abnormal responses due either initially to "shock" or later to release from central control.

Since the results of all experiments were identical, only one typical case is presented. The reading in the normal anesthetized cat is given in graph A (Fig. 3). Pressure readings were noted immediately before and after the introduction of air so that such instillations are readily recognized. Six increments each of 5 cc. of air were introduced into the rectal balloon. Filling was then stopped because the pressure had reached the limit which could be measured by our apparatus. No stretch responses were elicited from the rectal muscle by the sudden distention of the balloon. A few rhythmical waves of muscle contraction were seen after the addition of the second increment of air. The smaller waves were oscillations produced by respiratory activity. The rectal wall showed more resistance to distention than in the dead animal (Fig. 2B).

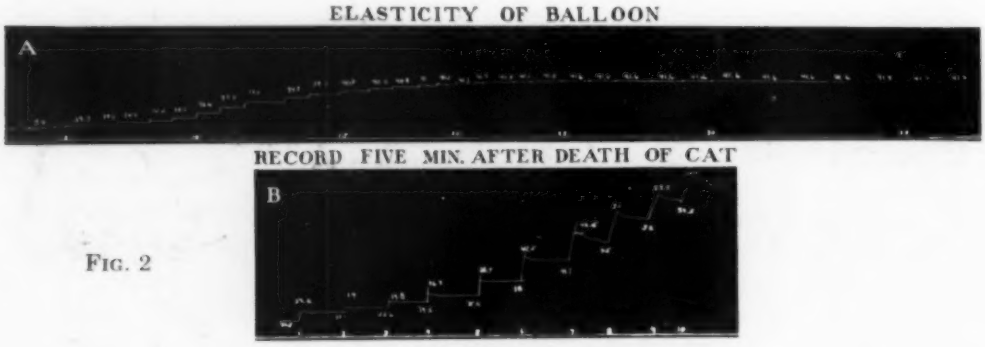


FIG. 2

The brain stem was then transected just above the level of the optic colliculi, and the anesthetic was stopped. A second record was made which is shown in graph B (Fig. 3). In this case nine increments of air were introduced. Superimposed upon the small respiratory waves, larger waves of contraction of the rectal muscle were visible. These were seen following the addition of the first three increments of air. They then diminished to start again with even greater amplitude as the rectum became distended. After the introduction of the seventh, eighth, and ninth quantities of air, a marked stretch response was elicited from the wall. Following the ninth instillation of air the pressure rose till the balloon was expelled. It appears from the graph that the rectal muscle was more irritable to stretch stimuli, and more waves of contraction occurred after section of the brain at this level than in the normal animal.

A second cut transected the brain stem between the optic and acoustic colliculi. Difficulty was encountered in inserting the balloon because of the resistance offered by the increased irritability of the rectal muscle. This record (graph C, Fig. 3) indicates that the rectum could not accommodate more than one increment of 5 cc. of air. The rectal wall contracted strongly in response to this stretch, producing two sharp, peaked waves of contraction. The pressure then fell, but slowly rose again and the balloon was expelled. It may be assumed that transection at this level resulted in a marked increase in tone of the rectal muscle which became hyperirritable to stretch. Diarrhea was observed in the animal at this phase of the experiments, and

may be interpreted as an increase in tone and irritability of the muscle in other portions of the gastrointestinal tract. The fourth record, shown in graph D, was made after the brain stem was transected in the upper part of the medulla below the vestibular nuclei. Ten increments of air were introduced into the balloon before the maximum pressure limit of our apparatus was reached. It will be recalled that only six increments could be instilled in the normal cat. The rectal wall was no longer hyperirritable. No rectal contractions and no responses to stretch were observed. Since the cut was made above the respiratory center, the respiratory phases were quite normal.

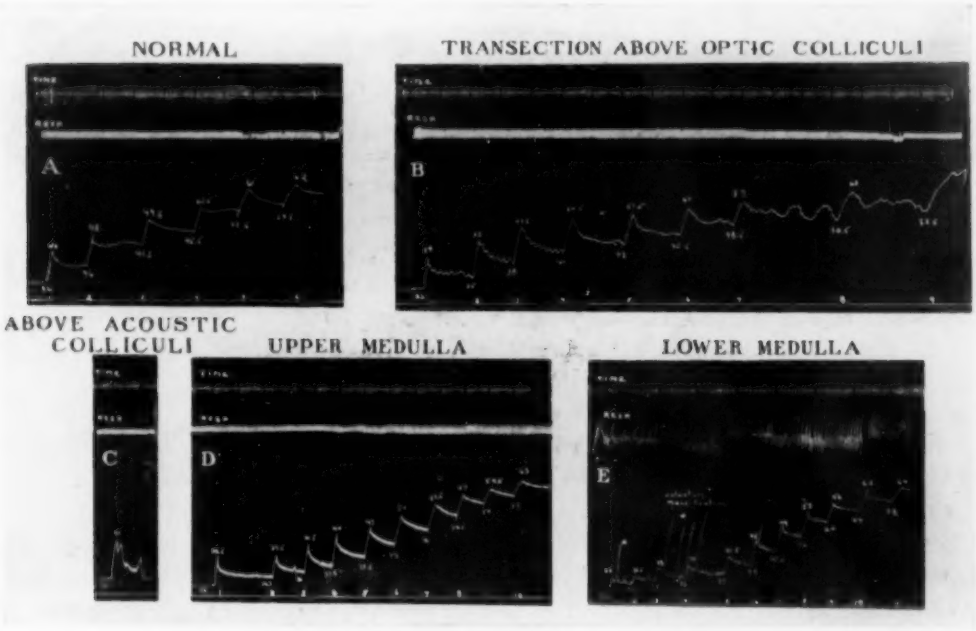


FIG. 3

The fifth record shown in this series (graph E, Fig. 3) was made after a transection through the lower portion of the medulla. Eleven increments of air could be introduced into the balloon. Again no stretch responses or rhythmic contractions were noted. The short spikes of pressure rise were due to spasmodic contractions of the striated muscle of the abdominal wall. At this level the cut was below the respiratory center; respiratory exchange was only made possible through automatic inflation of the lungs. The record of breathing is irregular because the diaphragm and intercostal muscles contracted strongly when they were stretched passively.

Other studies were made after section of the spinal cord in the thoracic region. These were quite similar to the records shown in graphs D and E.

DISCUSSION

Some years ago we demonstrated that tone in the smooth muscle of the urinary bladder was controlled by reflex arcs involving the midbrain (Lang-

worthy and Kolb, 1933). The technique of the experiments was similar to that employed here. After transection of the brain stem at the level of the optic colliculi, there was a marked increase of tone in the muscle. The stretch reflex was hyperactive, and the bladder would accommodate only a small amount of fluid. Then a strong contraction occurred which emptied the bladder completely.

In the present group of experiments we did not determine the changes in irritability of the rectal muscle after removal of the cerebral motor cortex alone upon one or both sides as we did in the case of the urinary bladder. However, from the result of transection of the brain stem just above and then behind the optic colliculi it would appear that in addition to the control exercised by the cerebrum there is a secondary mechanism for the control of tone at a lower level in the anterior end of the midbrain. It was only when the cut was carried to a level below the optic colliculi that the tonic reflex was completely released. This was also true in the case of the bladder. Even after the cerebral motor cortices had been removed bilaterally there was a further increase in tone after transection below the optic colliculi. From the experiments of Magnus one might suggest that this final release is due to removal of the influence of the red nuclei or of other nuclear masses at that level. The assumption may be made therefore, that there is in the region of the midbrain a mechanism controlling tone in the smooth muscle of the rectum. Its action is normally held in check by stimuli from the forebrain, and particularly from the region of the cerebral cortex. After this cortical and forebrain control is removed, the tonic center becomes overactive. The rectal muscle has increased tone and is abnormally responsive to stretch stimuli. After section below this tonic mechanism, tone is lost in the muscle. It no longer responds to stretch stimuli nor are spontaneous waves of contraction seen. In this portion of the brain there is an integration of tone in the striated muscle of the body. It seems likely that tone in the smooth muscle of the rectum is determined by reflex arcs similar to those controlling tone in the striated muscles of the body.

Summary. There is a tonic mechanism in the midbrain controlling the smooth muscle of the rectal wall. After transection of the brain stem just cephalic to the acoustic colliculi, the smooth muscle of the rectal wall becomes hyperactive to stretch stimuli and strong waves of contraction occur which expel the balloon from the rectum. After a lower section through the medulla, the stretch responses are lost, no contractions occur, the wall accommodates to a larger volume than normal, and the balloon is not expelled.

DENNY-BROWN, D., and ROBERTSON, E. G. An investigation of the nervous control of defaecation. *Brain*, 1935, *58:* 256–310.

FULTON, J. E. *Physiology of the nervous system*. New York, Oxford Univ. Press., 1938, xvi, 675 pp. (see p. 479).

LANGWORTHY, O. R., and KOLB, L. C. The encephalic control of tone in the musculature of the urinary bladder. *Brain*, 1938, *56:* 371–382.

LANGWORTHY, O. R., LEWIS, L. G., DEES, J. E., and HESSER, F. H. A clinical study of the control of the bladder by the central nervous system. *Bull. Johns Hopk. Hosp.*, 1936, *58:* 89–108.

WATTS, J. W. The influence of the cerebral cortex upon gastro-intestinal movements. *J. Amer. med. Ass.*, 1935, *104:* 355–357.